CLINICAL REVIEW

Application Type	NDA 20-727
Submission Number	20-727
Submission Code	N-000
Letter Date	December 23, 2004
Stamp Date	12/23/04
PDUFA Goal Date	6/23/05
Reviewer Name	Salma Lemtouni
Review Completion Date	4/15/05
Established Name	Hydralazine HCl and Isosorbide dinitrate
(Proposed) Trade Name	BiDil
Applicant	NitroMed, Inc.
Priority Designation	P
Formulation	Hydralazine 75 mg/Isosorbide dinitrate 40 mg
Dosing Regimen	t.i.d.
Indication	Heart Failure
Intended Population	African American

Table of Contents

List of Tables

List of Figures

Abbreviations

AA: African American
ACE-I: angiotensin converting enzyme inhibitor
AA: African American
AE: adverse event
AICD: automatic implantable cardiac defibrillator
ARB: angiotensin receptor blocker
BEST: Beta-blocker Evaluation of Survival Trial
BNP: brain natriuretic peptides
bpm: beat per minute
BSA: body surface area
BSA: body surface area
CABG: coronary artery bypass graft
CAD: coronary artery disease
CCB calcium channel blockers
CCB: calcium channel blocker
CHF: congestive heart failure
CI: confidence interval
CKMB: creatinine kinase
CO: cardiac output
COPD: chronic obstructive pulmonary disease
COSTART: coding symbols for thesaurus of adverse reaction terms
CRF: case report form
CVA: cerebrovascular accident
CVD: cardiovascular disease
D50W: 50% dextrose in water
DBP: diastolic blood pressure
DSMB: data and safety monitoring board
DVT: deep venous thrombosis
EF: ejection fraction
ER: emergency room
ETOH: alcohol
GCP: good clinical practices
GERD: gastro-esophageal reflux disease
HF: heart failure

HR:	heart rate
HYD:	hydralazine
ICAC:	Independent Central Adjudication Committee
ICD:	implantable cardiac defibrillator
ISDN:	isosorbide dinitrate
ITT:	intention-to-treat
LBBB:	left bundle branch block
LOCF:	last observation carried forward
LVEF:	left ventricular ejection fraction
LVEF:	left ventricular ejection fraction
LVH:	left ventricular hypertrophy
LVID:	left ventricular internal diameter
LVIDD:	left ventricular internal diameter in diastolic
MLHF	Minnesota living with heart failure
msec:	millisecond
MVO_2:	maximum oxygen consumption
NYHA:	New York heart association
MVO_2:	maximum oxygen consumption
NO:	nitric oxide
OL:	open label
PCI:	percutaneous coronary intervention
PTCA:	percutaneous transluminal coronary angioplasty
PVC:	premature ventricular contraction
QOL:	quality of life
q.i.d.:	four times daily
SAE:	serious adverse event
SBP:	systolic blood pressure
SD:	standard deviation
SLE:	systemic lupus erythematosus
SOLVD:	Studies of Left Ventricular Dysfunction
TIA:	transient ischemic attack
t.i.d.:	three times daily
UTI:	urinary tract infection
V-HeFT:	Vasodilator-Heart Failure Trial
WBC:	white blood count

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The A-HeFT study was prematurely terminated for a significant reduction of mortality on BiDil. Even though less data than planned was collected as a result of early termination, A-HeFT was able to meet its primary endpoint of a significant favorable change in the mean of the composite score of mortality, first hospitalization for HF and QOL on BiDil compared to placebo.

As to the secondary endpoints, changes in the mean of individual scores of mortality and hospitalization were also significantly different between BiDil and placebo.

The incidence of and the time to death and time to first hospitalization for HF were significantly different between the BiDil and the placebo arms.

Except for headache and dizziness, subjects taking BiDil experienced less adverse events than subjects taking placebo. Headache and dizziness are known to be associated with organic nitrates.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

BiDil is a fixed combination of hydralazine (HYD), a drug approved for essential hypertension, and isosorbide dinitrate (ISDN) approved for the prevention of angina pectoris. BiDil was to be taken orally t.i.d which is the equivalent of 225 mg of HYD and 160 mg of ISDN.

A-HeFT was a randomized, placebo-controlled trial that was designed to enroll 1100 African American subjects with NYHA classes III and IV heart failure, and follow them up to 12 months to evaluate the effect of BiDil on all cause mortality, hospitalization and the quality of life and its safety in this ethnic group.

A total of 1050 patients were randomized to BiDil (49%) and placebo (51%), and 71%, 61%, 50%, 42%, 33% and 30% were exposed to the study drug for 3, 6, 9, 12, 15 and ≥ 15 months respectively.

Findings from two other studies, V-HeFT I and V-HeFT II are used as secondary source of the safety assessment and the effect of BiDil in the African American HF sub-population.

1.2.2 Efficacy

The primary endpoint of the A-HeFT trial was the mean change in the composite score of death (-3 or 0), hospitalization (-1 or 0) and QOL (-2 or +2). Secondary endpoints included the mean change in the individual scores of the components, and the rate of and time to event of death and first hospitalization for HF.

The composite score used in this trial was not studied or validated in any population. It weighed the components based on no data that would enable the translation of the differences in individual and/or population scores into clinically meaningful benefits. For instance a subject who was hospitalized and whose QOL deteriorated by > 10 points would contribute as much to the overall score as a patient who died. There is no data that would tell us

whether these two outcomes, which are known to have different meanings at the individual level, are either equivalent at the population level or perceived in a similar way by the medical community.

However, given that BiDil was shown to have an effect on the scores of the main components, the composite score and the weight attributed to its components becomes less critical.

The findings of the A-HeFT study support a beneficial effect of BiDil on all-cause mortality and hospitalization for HF in African American patients.

1.2.3 Safety

The safety of BiDil in the study population was derived from analyses comparing the effect of exposure to BiDil for an average of 6 months in 519 subjects and to placebo in 532 subjects.

Overall serious adverse events were experienced at a similar rate in both-treatment arms, 35% on BiDil and 34.7% on placebo. The following serious adverse events were observed on BiDil at a slightly higher rate than on placebo: ventricular tachycardia 2.7% (14) vs. 1.5% (8), hypotension 1.5% (8) vs. 0.6% (3), dizziness 1.4% (7) vs. 0.0%, cerebral ischemia 1.0% (5) vs. 0.2% (1), syncope 2.1% (11) vs. 1.5% (8), and cellulites 1.2% (6) vs. 0.4% (2).

There were more discontinuations as a result of adverse events on BiDil compared to placebo 21.1% (109) vs. 12.0% (63). More than half the discontinuations on BiDil were accounted for by headache (7.4%) and dizziness (3.7%). Other adverse events that led to discontinuation at a higher rate on BiDil compared to placebo include asthenia 2.3% (12) vs. 0.2% (1), chest pain 1.5% (8) vs. 0.4%) (2), nausea 1.5% (8) vs. 0.4% (2), and hypotension 1.4% (7) vs. 0.4% (3).

1.2.4 Dosing Regimen and Administration

The titration schedule of BiDil in the A-HeFT trial seemed to be brisk and as a result, almost twice as many BiDil as placebo patients discontinued the study drug, and more than half of these were due to headache and dizziness, a good proportion of which could have been avoided had the titration proceeded more cautiously.

1.2.5 Drug-Drug Interactions

No formal assessment of interactions of BiDil with other drugs was undertaken. Of concern are some beta-adrenergic antagonists which were found to interact with hydralazine.

1.2.6 Special Populations

The effect of BiDil in heart failure in this study was assessed solely in African American patients. The results of the A-HeFT study will not be generalizable to other ethnic group.

Subgroup analyses showed that BiDil was as efficacious and relatively safe in elderly and in female subjects as it was in younger and in male subjects.

BiDil was not studied in pediatric subjects, and a request for a waiver was submitted with this application. The Division abstained from granting the sponsor a waiver until the application is fully reviewed, and instead granted them a deferral.

2 INTRODUCTION AND BACKGROUND

2.1 Rational for the A-HeFT Trial

With respect to medical outcomes, African-American patients are diagnosed with HF at a higher rate than whites. Death rate from cardiovascular disease in AA in the 1990s was estimated to be 353 in males and 226 in females, while that of Caucasians was 244 in males and 135 females per 100,000.

It is hypothesized that in addition to socioeconomic factors, and differences in access to care and disease management, other factors including response to pharmacological therapies contribute to the observed differences. Some of the factors that were either studied or advanced as potential determinant factors in the differences observed include:

--salt sensitivity and low-renin hypertension;

--left ventricular hypertrophy (LVH) disproportionate to afterload;

--microvascular ischemia in the absence of significant epicardial CAD;

--higher prevalence of hypertension and LVH;

--higher incidence of normal coronary arteries in HF despite a high prevalence of risk factors for coronary atherosclerosis;

Secondary post-hoc analyses of SOLVD, VHeFT II and BEST data showed differential effect by race in the following:

--enalapril with regard to HF-related hospitalization in SOLVD, Table 1 page 14, and a change in the QOL in VHeFT II, Table 3 page 14,

--bucindolol with regard to survival in BEST (data not provided).

On the other hand, carvedilol has not been associated with an ethnic effect in HF (data not provided).

The explanation advanced for the difference in response of AA hypertensive subjects to ACE inhibitor therapy, and the observation that AAs fare better with diuretics than with either ACE inhibitors or beta-blockers are suspected to be partially related to nitric oxide (NO) insufficiency in this population. The same explanation is advanced for the apparent reduced responsiveness of AA HF subjects to these medications.

Nitric oxide insufficiency, secondary to either reduced production of NO or its inactivation by overabundant reactive oxygen species as a cause of the reduced responsiveness of AA to the available HF therapies was expected to be addressed by treatment with BiDil which is believed to have both characteristics of an NO donor and an antioxidant.

HYD/ISDN was associated with lower mortality in the study population of the VHeFT I compared to placebo and prazosin but this did not reach statistical significance. In the VHeFT II, HYD/ISDN was shown to be statistically significantly inferior to enalapril in reducing mortality at 2 years. Post-hoc analyses have shown that HYD/ISDN was associated with a reduction of mortality in black patients in V-HeFT I, Table 2 page 14, and mortality trends in the V-HeFT II were reversed in blacks toward no difference between BiDil and enalapril while enalapril was superior to BiDil in whites, Table 3 page 14 and Table 28 page 42.

The following tables summarize the findings of the post-hoc analyses of the SOLVD and VHeFT I and II, and provide the rational for the conduction of A-HeFT.

Table 1. Ethnic Reanalysis of SOLVD Trial

	Blacks		Whites		Racial Interaction
	Risk Ratio* (CI)	p-Value	Risk Ratio* (CI)	p-Value	p-Value
All-Cause Mortality	0.92 (0.72 - 1.18)	ns	0.95 (0.76 - 1.18)	ns	p=0.7
Cardiovascular Death	0.92 (0.71 - 1.20)	ns	0.96 (0.76 - 1.22)	ns	p=0.6
Hospitalization for CHF	0.95 (0.74 - 1.23)	ns	0.54 (0.41 - 0.71)	p<0.001	p=0.005
Death or Hospitalization for CHF	0.91 (0.75 - 1.12)	ns	0.75 (0.62 - 0.91)	p<0.01	p=0.2

* Enalapril vs. placebo

Table 2. VHeFT I Data Summary Table[1]

	Blacks			Whites			Racial Interaction p-Value
	BiDil	Enalapril	p-Value	BiDil	Enalapril	p-Value	
Annual Mortality Rate (%)	9.7	17.3	0.04	16.9	18.8	ns	0.11
Mortality Risk Ratio	0.341	N/A	0.004	0.746	N/A	0.11	0.074
Change in EF at 12 Months vs. Baseline (%)	0.023	0.0136	0.82	0.081	0.012	0.02	0.23
Change in MVO_2 at 12 M (mL/kg/min)	1.25	-0.394	0.068	0.681	-0.162	0.12	0.69

Table 3. VHeFT II Data Summary Table[1]

	Blacks N = 215			**Whites N = 574**			**Racial interaction p-value**
	BiDil	**Placebo**	**p-value**	**BiDil**	**Placebo**	**p-value**	
Annual Mortality Rate (%)	12.9	12.8	ns	14.9	11.0	0.02	0.25
Mortality Risk Ratio	0.95	N/A	0.83	1.48	N/A	0.0087	0.10
Change in EF @ 12 M (%)	2.97	1.32	0.34	3.86	2.48	0.12	0.82
Change in MVO_2 at 12 M (mL/kg/min)	0.79	0.01	0.15	0.24	-0.42	0.058	0.47
Change in QOL at 12 M	-0.67	1.04	0.04	0.24	0.26	0.97	0.09

[1] Analyses completed by the sponsor

2.2 Product Information

BiDil is a fixed combination of hydralazine hydrochloride, a peripheral vasodilator with antihypertensive properties, and diluted isosobide dinitrate, an organic nitrate with a vasodilating action on both arteries and veins. The proposed name is either BiDil or ZiDil. If approved, per the proposed label, BiDil will be indicated for the treatment of chronic heart failure as an adjunct to standard therapy in black patients who are intolerant or have a contraindication to ACE inhibitors .

2.3 Currently Available Treatment for Indication

Medications that have an indication for heart failure treatments in the US include ACE-I, ARBs and beta-adrenergic antagonists. The effect of these drugs in AA subjects has not been evaluated with adequate power, and therefore not quantified in this subpopulation. It is known that these drugs do not have the same effect in the treatment of hypertension in AA as they do in White subjects.

2.4 Availability of Proposed Active Ingredient in the United States

Isosorbide dinitrate is an organic nitrate available in a generic formulation for the prevention of angina pectoris as sustained release capsules of 40 mg.

Hydralazine hydrochloride is also available in a generic formulation for the treatment of essential hypertension alone or as an adjunct therapy as tablets of 10, 25, 50 and 100 mg.

2.5 Pre-submission Regulatory Activity

The original NDA 20-727 was submitted in July of 1996 for BiDil, and the application initially proposed the use of BiDil for a mortality claim in CHF patients who were intolerant to ACE-I. This was later revised to a claim for symptomatic relief for all CHF patients.

In February of 1997 the BiDil application went before Cardiac and Renal Drugs Advisory Committee who voted 9 to 3 to not approve it because the committee did not believe that the data submitted met the regulatory standard for approval.

A non-approvable letter was sent to the sponsor on July 2, 1997. This letter raised chemistry and pharmacokinetics deficiencies, listed pre-approval requirements and responded to requests by the sponsor, and these included:

> --the concern that the sponsor has not adequately addressed the possibility of an interaction between the drug substances to form N-nitrosamines, products that have the potential to be carcinogenic;
>
> --the Division's denial of a bioavailability waiver for the 37.5/20 and 75/20 dose strengths because the 37.5/10 strength showed a slower dissolution performance compared to the former strengths;
>
> --the statement that a proposal for inclusion of information regarding food effect on HYD/ISDN based on published literature could not be acceptable, and that a food effect study, using the to-be marketed formulation of BiDil would be required to support any statement relating to the effect of food on administration of BiDil;

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the sponsor's responses to the pharmacokinetic issues, found the responses acceptable except for the response pertaining to the effect of food on BiDil for which the FDA recommended the inclusion in the label of the following text: "No information is currently available regarding the effect of food on BiDil tablets" which was acceptable to the sponsor.

In the minutes of the end-of-phase-II meeting, the Division expressed the concern that the fixed dose combination would produce tolerance because it would deliver ISDN continuously, a regimen that per the ISDN label is to be avoided. The Agency also stated that animal studies showing that hydralazine protected against tolerance to ISDN were not enough and that human data were needed for support.

2.6 Animal Pharmacology/Toxicology

2.6.1 See Dr. Defelice's Review

3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

3.1 Sources of Clinical Data

Data used for the evaluation of efficacy and safety came from one main source, the A-HeFT study. Additional material used for the review of this application included Agency medical and statistical reviews of the V-HeFT I and V-HeFT II trials plus subgroup data of these two studies provided by the sponsor a as part of the submission and upon request by the reviewer..

3.2 Tables of Clinical Studies

Table 4. Summary of clinical studies

Study	Design	Type of subjects	Treatment		Duration	Dose	Relevance of Data
			BiDil	Comparator			
A-HeFT	R, DB, PC	AA with HF	518	Placebo 532	6 M	75/40 mg x 3	++++++
V-HeFT I	R, DB, PC	Males with HF	186	Placebo 273	≥ 2 years	75/40 mg x 4	+++
V-HeFT II	R, DB, AC	Males With HF	401	Enalapril 403	62 M	75/40 mg x 4	++
CB-02	R, OL, CO	Healthy males	149	--	[1]	37.5/40 mg	+
CB-01	R, OL, CO	Healthy	12	--	[1]	75/40 mg	-

[1] Single doses interspaced with a washing period;

3.3 Review Strategy

A paper application was submitted and used for review. A-HeFT was reviewed in greater detail than V-HeFT I and II. For efficacy, A-HeFT was the only source of review, but for safety, additional data from the V-HeFT studies were used.

3.4 Data Quality and Integrity

3.5 Compliance with Good Clinical Practices

The study was conducted in the US and per the study report, the sponsor asserts that they had adhered by the guidelines of GCP in conducting A-HeFT.

The protocol violations that occurred during A-HeFT are summarized in Table 7 page 28.

3.6 Financial Disclosures

4 CLINICAL PHARMACOLOGY

4.1 See Reviews of Drs. Hinderling and Velazquez

5 INTEGRATED REVIEW OF EFFICACY

5.1 Indication

The proposed indication for BiDil is the treatment of CHF as an adjunct to standard therapy in black patients who are intolerant or have a contraindication to ACE-Is.

5.1.1 Purpose and Study Objectives

The trial was intended to provide additional data in support of the findings of VHeFT subpopulation analyses and to support an NDA.

Three main objectives were specified:

--To demonstrate that BiDil is superior to placebo with regard to a composite score made up of 3 component scores including the QOL, hospitalizations and all-cause mortality;

--to assess the safety and tolerability of BiDil in AA heart failure patients;

--to demonstrate favorable trends in one or more of the individual components of the primary composite endpoint, the total number of hospitalizations, the duration of hospitalizations, unscheduled office and/or emergency room visits, and the echo parameters of cardiac size and function;

5.1.2 Methods

A-HeFT, the placebo-controlled trial of fixed dose of BiDil added to standard therapy in African-American patients with heart failure, was conducted to assess the effect of BiDil mortality, first-time hospitalization rates, and the quality of life.

V-HeFT I and II used two formulations that are different from the fixed dose used in A-HeFT.

A concern regarding the bioequivalence of the formulations used in V-HeFT to the combination formulation used in A-HeFT was raised in the End-of-Phase-II meeting held in November of 1992. Therefore the post-hoc analysis results of efficacy in the two trials will not be used for support of efficacy.

5.1.3 General Discussion of Endpoints

5.1.3.1 A-HeFT Study Endpoints

5.1.3.1.1 Primary Efficacy Endpoint

This is a composite of three scores, death, hospitalization for heart failure (adjudicated), and change in QOL (MLHF questionnaire) at 6 months or last available assessment.

Death = -3 vs. alive at end of trial = 0

Hospitalization for HF = -1 vs. no hospitalization = 0

Change in QOL

Improvement ≥ 10 units = +2

Improvement ≥ 5 and < 10 units = +1

Improvement < 5 units = 0

Worsening ≥ 10 units = -2

The final score ranged between -6 if a patient's QOL worsened by ≥10 units, was hospitalized and died; and +2 in a patient was neither hospitalized nor dead and his QOL improved by ≥ 10 units.

In the primary analysis the worst case scenario was to be assumed for missing data and the secondary analysis was to use only available data with no imputed values.

Death: All cause mortality was to be used in the primary efficacy analysis. Death was to be adjudicated by an Independent Central Adjudication Committee (ICAC) and classified by cause including HF and other cardiac or non-cardiac cause, and as sudden or non-sudden death.

Hospitalization: Occurrence of the first hospitalization for HF was to be counted, and like death, the cause was to be adjudicated;

Hospitalization for HF: was defined as such if it lasted more than one calendar day, and the primary reason was worsening of signs or symptoms of HF and the patient required IV medications or other non-parenteral medication given specifically for HF;

QOL: the MLHF questionnaire administered at 6 months or last available measurement if the 6-month one was not;

5.1.3.1.2 Secondary efficacy parameters

They consist of:

- Individual components of the primary composite;
- Death:

  --from any cause;

  --from HF;

  --from cardiac causes other than HF;

  --sudden vs. non-sudden;
- Total number of hospitalizations

  --for HF;

-- for any cause;

- Total days in hospital;
- Overall QOL throughout the trial;
- Number of unscheduled emergency room and/or office/clinic visits (cause adjudicated by ICAC);
- Echocardiogram parameters including LVEF, LVIDD, and LV wall thickness. Echocardiograms were to be inspected for readability by a core laboratory and read by a blinded external expert;
- BNP levels;
- Newly recognized need for cardiac transplantation; this was to be adjudicated by the ICAC and data from patients undergoing transplant during the trial were to be censored;

5.1.3.1.3 Discussion of A-HeFT Endpoints

A-HeFT was the first study to ever use the composite score (discussed in 5.1.3.1.1 page 18), and because of the lack of an estimate of its variability in the intended study or any other population, criteria were built in the design to allow for interim analyses to adjust the sample size.

The primary endpoint would have been difficult to defend had the study not won on the main components of the composite endpoint because it would be difficult to interpret the meaning of a score in terms of a clinical benefit. The other issue would have been whether the components were weighted proportionally to the clinical weight each one has in the study population.

Secondary endpoints included components of the primary composite endpoint, endpoints that revolve around death and hospitalization, unscheduled visits to the ER and/or office/clinic, echocardiographic parameters and markers of deterioration most of which are clinically relevant to heart failure patients.

The endpoints that were planned to be adjudicated are cause of death, all hospitalizations, unscheduled ER or Office visits and new heart transplant listing.

5.1.3.2 V-HeFT Study Endpoints

See 5.1.5.2 page 22 and 5.1.5.3 page 22;

5.1.4 Study Population

5.1.4.1 A-HeFT Study Population

Eleven hundred patients with NYHA class III-IV and stable chronic heart failure were required to meet the primary objective of A-HeFT.

They were to have a resting LVEF $\leq$ 35% or LVIDD $\geq$ 2.9 cm/m^2 BSA (or > 6.5 cm) plus LVEF < 45% (by echocardiogram obtained within 6 months), and to be, per the investigator, symptomatically stable for at least 3 months and on a stable treatment regimen for at least 2 weeks (at least 3 months for beta-blockers)

To be excluded were subjects with significant valvular disease, hypertrophic obstructive cardiomyopathy, active myocarditis, uncontrolled hypertension or symptomatic hypotension; subjects who have had unstable angina, MI, cardiac surgery or PTCA, cardiac arrest, life threatening sustained ventricular tachycardia requiring intervention unless treated with an ICD, or stroke within 3 months of screening; subjects who have CAD likely to require CABG or PTCA; subjects who have rapidly deteriorating or uncompensated HF that render cardiac transplantation likely during the ensuing year; subjects who received parenteral inotropic therapy within one month; or subjects who have significant hepatic, renal or other condition that might limit survival over the ensuing one year;

5.1.4.2 V-HeFT Study Populations

See 5.1.5.2 page 22 and 5.1.5.3 page 22;

5.1.5 Study Design

5.1.5.1 Pivotal Trial: "A-HeFT (African-American Heart Failure Trial), a Placebo-Controlled Trial of BiDil Added to Standard Therapy in African-American Patients with Heart Failure"

This is a multicenter, randomized, double-blind, placebo-controlled parallel group study in AA patients in which eligible subjects were to be randomized after a 2-week run-in period to t.i.d. BiDil or identical appearing placebo within strata of beta- or no beta-blocker therapy.

The original protocol of A-HeFT (reviewed under IND 41816) was completed on 3/15/01, and after a little over 3 years and ten amendments, the final A-HeFT protocol was completed (06/08/04, date of the last amendment), just one month before termination of the trial.

Mortality was the main endpoint. Other endpoints were adjudicated by an Independent Central Adjudicated Committee.

The investigational therapy, BiDil was supplied as a fixed-dose combination of ISDN 20 mg plus HYD 37.5 mg (referred to as BiDil 20 Tablets). One tablet of BiDil was to be initiated t.i.d. and if tolerated 3 to 5 days later the dose is to be increased to 2 tablets t.i.d thus delivering an initial dose of 60/112.5 mg/day and maintenance dose of 225/160 mg/day of ISDN/HYD. If not well tolerated, either BiDil or background medication could be adjusted as appropriate. BiDil could be administered as ½ and 1 ½ tablets t.i.d. as well.

BiDil could be titrated down to avert adverse events. For symptomatic hypotension, it was suggested to adjust other anti-hypertensive therapies before altering the dose of BiDil. Following a dose adjustment, another dose titration was to be attempted and if the target dose was not tolerated, the maximally tolerated dose was to be administered.

The plan was to follow patients up to a maximum of 18 months or until the last randomized patient has completed 6 months post-randomization, but because the study was terminated early as a result of a statistically significant difference in mortality between the two treatment arms, 38.7% and 36.8% of the BiDil and placebo groups had less than 6 months exposure.

Study design is shown schematically in figure below

Figure 1. Schematic of Study Design (sponsor's schema)

	Screening	Baseline	Titration	Treatment & Follow-up			
Visit No.	-1	0	0+	1	2	3*	4+ & Final Visit*
Day/wk/mo. No.	-2 Wk.	0	3-5 Days	3 Mo.	6 Mo.	9 Mo.	12 Mo.

* All patients seen every 3 months until either a maximum of 18 months or until the last patient completes visit No. 2.

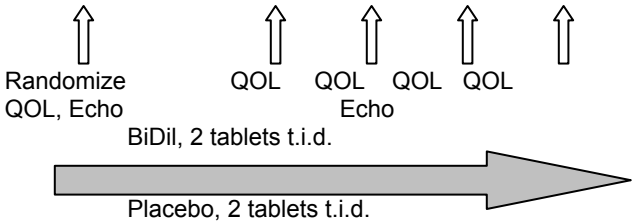


Table 5. Study flow chart (Sponsor's chart)

	Screen	Baseline	Titration	Treatment & Follow-up			
Visit No.	-1	0	0+	1	2	3	4+ & Final Visit
Day/wk/mo. No.	-2 Wk.	0	3-5 Days	3 Mo.	6 Mo.	9 Mo.	12 Mo.
Informed consent	X						
Incl./Excl. criteria	X	X					
Medical history	X						
Complete physical exam	X				X		
Review qualifying LVEF & LVIDD	X						
Serum or urine pregnancy	X						
NYHA class	X	X		X	X	X	X
Concomitant medications	X	X		X	X	X	X
Adjust background therapy	X		X	X	X	X	X
Interim history		X	X	X	X	X	X
Brief physical exam		X		X	X	X	X
Confirm stability		X					
ECG		X					
Clinical chemistry		X					
Hematology		X					
Urinalysis		X					
Echocardiogram[1]		X			X		

	Screen	Baseline	Titration	Treatment & Follow-up			
Visit No.	-1	0	0+	1	2	3	4+ & Final Visit
Day/wk/mo. No.	-2 Wk.	0	3-5 Days	3 Mo.	6 Mo.	9 Mo.	12 Mo.
BNP		X			X		
QOL		X		X	X	X	X
Randomize & start study medication		X					
Dispense study medication		X		X	X	X	X
Titrate study medication[2]			X	X	X	X	X
Schedule next visit	X	X	X	X	X	X	X
Document Adverse Events		X	X	X	X	X	X

[1] Obtain in all patients for baseline and follow-up LVEF and LVIDD. Baseline results not used for "qualifying".

[2] May repeat titration visit as needed and may adjust study medication and background therapy anytime as needed.

5.1.5.2 V-HeFT I "Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure"

This was a controlled parallel group, placebo, ISDN/HYD and prazosin, multicenter trial that randomized 642 patients with chronic CHF, NYHA class II and III who were on a background therapy of digitalis and diuretics.

The study randomized only male patients who had a history and physical consistent with left ventricular failure and with a limitation of exercise tolerance because of dyspnea and/or fatigue beginning at least 3 months prior to screening. Excluded were patients with hypertrophic cardiomyopathy, hypertensive patients requiring treatment with drugs other than diuretics, chronic beta blocker therapy, and therapy with vasodilator drugs. The double blind treatment period was to last at least 2 years. Major endpoints included two-year mortality, the number and duration of hospitalization for cardiovascular causes, maximum oxygen consumption during peak exercise, maximum treadmill exercise time on graded test, and duration of exercise on submaximal test.

5.1.5.3 V-HeFT II "A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure"

IND 16-960 submitted on 11/25/85 described the study in a protocol as a multicenter, randomized, double-blind, parallel, active-controlled trial in patients with CHF. Patients were randomized to either HYD/ISDN or enalapril and the duration of the study was projected to be of 62 months with a minimum of 6 months.

Inclusion criteria were similar to those of V-HeFT I with additional specifications including EF < 0.45 by radionuclide method, LVID > 2.7 cm/m^2 at diastole on echocardiography, cardiothoracic ratio ≥ 0.55, and reduced exercise tolerance. Exclusion criteria were similar to

those of V-HeFT I plus diastolic blood pressure ≥ 105 mmHg or hypertension requiring non-diuretic therapy and dependence on chronic therapy with calcium channel blocker.

Major study endpoints were similar to the V-HeFT I study plus changes in the QOL and oxygen consumption at the anaerobic threshold.

Four hundred and one patients were randomized to HYD/ISDN and 403 to enalapril.

5.1.5.4 Adequacy of Study Design

The design of the pivotal trial was not the required design of a combination product which is usually factorial and compares the combination product to each of the components and placebo. The A-HeFT trial compared BiDil to placebo only. Therefore, we will not be able to know for sure whether the combination is necessary for treatment of the studied condition in the studied population, or either component would have been as effective as and somewhat safer than the combination.

5.1.6 Treatment Plan

In A-HeFT, a target maintenance dose of 120 mg/day of ISDN and 225 mg/day of HYD was to be achieved through 2 BiDil tablets taken t.i.d. If the target maintenance dose was not tolerated, the maximally tolerated dose was to be given by adjusting the number of tablets and/or the portion of a tablet to be taken t.i.d. Background medication was to be adjusted as clinically indicated to increase the likelihood of study drug toleration. Another attempt to titrate the dose to target level in subjects who failed to reach it was to be made within the first month of treatment.

5.1.7 Concomitant Medication

Study subjects were to be symptomatically stable and receiving a stable treatment regimen for at least 2 weeks prior to randomization. The treatment regimens of these patients may include spironolactone, digitalis, or other at the investigator's discretion. Beta blockers were to have been taken for at least 3 months.

Except for patients on phosphodiesterase-5 inhibitors, patients on other medications especially those with potentially significant hemodynamic effects maybe enrolled as long as the regimen of administration was to remain stable for the duration of the trial.

5.1.8 Statistical Methods

The following hypothesis was the basis for the test of superiority of BiDil over placebo:

H_o: $\mu_B = \mu_P$ versus H_a: $\mu_B \neq \mu_P$

μ_B and μ_P are mean composite scores for BiDil and placebo.

5.1.8.1 Primary Efficacy Analyses

The primary analysis was to consist of a comparison of the mean composite score on BiDil to that on placebo using a 2-sample t-test, and constructing a two-sided 95% CI.

ANCOVA was to be used to test for the effect of BiDil controlling for baseline characteristics. The covariates that were to be considered were age (< 65 and ≥ 65), sex, and beta-blocker and ACE inhibitors categories (yes/no). Because the centers were numerous

and the number of subjects per center was small, treatment effect was to be examined across centers using descriptive statistics only.

Summary tables and figures were to include summary statistics of the composite score by treatment groups, and by age, sex, center, and beta-blocker and ACE inhibitors intake.

BiDil was to be considered superior to placebo and to have a treatment effect on the composite score if the null hypothesis above was rejected.

5.1.8.2 Secondary Efficacy Analyses

The consistence and robustness of the treatment effect was to be tested using secondary outcome measures. Two sample t-tests and ANCOVA modeling were to be used for continuous parameters, and Fisher's Exact tests (or Chi-Square tests where appropriate) and logistic regression models were to be used for binary parameters.

5.1.8.3 Analyses Populations

Intent to treat population or full analysis set of patients that consisted of all randomized patients was to be used as the primary efficacy population.

Analyses using the per-Protocol population were to be used for sensitivity analysis. Included were patients who have taken at least one dose of study drug, were still taking at least ½ tablet per day, have completed at least 3 months of treatment, have an QOL assessment without any major deviation from the protocol, and who's compliance $\geq$ 60% (compliance is computed as 100 times the ratio of tablets consumed to the required number prescribed).

For safety, all patients who were randomized and have at least one post baseline safety measure were to be included in the safety analysis.

5.1.8.4 Analysis Time Points

Analysis of the composite score was to use component scores at endpoint, the latter been defined as "death" or "no death" any time after randomization, "first hospitalization" or "no hospitalization" any time after randomization, and QOL at 6 months (or last measurement available if earlier than 6 months).

5.1.8.5 Handling of Missing Data

For the primary analysis, a worst score was to be assigned to components of the composite endpoint with missing values. Patients who were lost to follow-up were to be assumed to have died with a score of -3, to have been hospitalized (if they have not already being before loss to follow-up) with a score of -1, and their QOL to have worsened by $\geq$ 10 units and scored as -2 if they had no post randomization QOL measurement.

For secondary analyses, only available data was to be used with no imputation for missing data. Characteristics of drop-outs were to be compared between treatments, and characteristics that significantly differentiate drop-outs from completers were to be controlled in ANCOVA models.

Other analyses deviating from the original worst case scenario assignment to missing data were planned post-hoc and these include three types:

--The first analysis was to use the LOCF for QOL (up to 6 months), HF hospitalization and survival, and the worst score imputation to be used only for QOL, and only when a post-baseline value is unavailable.

The second analysis is similar to the first except that the LOCF value is not limited by the 6-month QOL.

The third analysis was to be conducted on a subset of the ITT population, 951 subjects who were randomized on or before April 19, 2004 and who have had the opportunity for a three-month QOL assessment.

5.1.8.6 Background and Demographic Characteristics

They were to be compared between treatment groups. It was stated that in the case an imbalance in baseline characteristics occurred, the treatment effect might be reassessed including the unbalanced characteristics in an ANCOVA model to increase the precision of its estimate.

5.1.8.7 Interim Analyses

No formal analyses were planned, but they were incorporated to determine whether the sample size was adequate. Two interim analyses were to be conducted, the first when 25% (150) and the second when 50% (300) of the patients have completed 6-month follow-up. The generated results were to be reviewed by the DSMB only. The sample size was to be re-estimated, using the Cui, et al. method, to provide an 80% power to detect an effect at a two-sided significance level of 0.02. It was decided that the sample size was to be formally adjusted only after the second interim analysis. The same method used to estimate the standard deviation for sample size calculations (described below) was to be used for sample size re-estimation.

The study was to be treated as a group sequential design (with K=3 Looks total) since the analyses were to be used for sample re-estimation and not to stop early for efficacy. Using the O'Brien-Fleming Boundaries, the two-sided p-values required for statistical significance were 0.00001 at Look 1, 0.0052 at Look 2, and 0.048 at the final Look.

5.1.8.8 Sample Size

For lack of data regarding the variability of the composite score, the estimation of the sample size relied on previous data from studies including VHeFT II that was designed to detect (with 80% power and a two-sided alpha of 0.05) a difference equivalent to 22.8% of a standard deviation of similar measures with 300 patients in each arm.

Using similar measures, the standard deviation of the proposed composite score was estimated to range between 1 and 2 units, and it was assumed that the study had adequate power to detect a difference of less than ½ a unit.

5.1.9 Protocol Amendments

There were ten amendments to the protocol most of which concerned the inclusion/exclusion criteria, for detail of the amendments, see 9.1. Some of these included a change in the cutoff of the LVEF, in the duration of pre-randomization beta-blocker intake, in the requirement of length of time the patient was in NYHA class III-VI before screening; the addition of a

LVEF criteria if LVIDD was to be used as an inclusion criteria; the elimination of the requirement of prior hospitalization; and forbidding current use of phosphodiesterase-5 inhibitors.

LV wall thickness assessment was added to echocardiographic measurements of LVEF and LVIDD; Echocardiographic measurements were to be done only at baseline and at 6- months instead of every three months; and reading of echocardiographic assessments were to be completed by an external expert instead of a core laboratory;

5.1.10 Post Hoc Changes

After the termination of the study the sponsor requested the addition of analyses termed "sensitivity analyses" in which missing data were to be handled differently than originally planned. The worst score was no longer to be imputed for survival and hospitalization and it was to be imputed for the QOL only if a post-baseline value was missing.

5.1.11 Results

5.1.11.1 Study Conduct

5.1.11.1.1 Interim Analyses

There were six DSMB meetings held. The first on March 19, 2002 after 221 subjects have been randomized. During this meeting the DSMB charter was discussed and it was agreed upon that the DSMB was to remain blinded until a decision was imminent. An overview of the sample size reassessment plan was presented, and it was decided that the first DSMB interim analysis was to be conducted when the first 150 patients have completed six-months of follow-up, and that an interim analyses assessing the sample size was to be conducted for the second, August 23, 2002 meeting. The new QOL scoring system was also discussed and it was decided that QOL analyses would be performed first using all participants who had 6-month QOL assessments, and they would be repeated using participants who have at least a 3-month QOL assessment.

At the second, August 23, 2002 DSMB meeting, only 137 participants had 6-month follow-up data. Results of an interim analysis were presented to the DSMB for a first look at the data. It was decided that next meeting would be scheduled when 300 patients have completed six-month visit.

The third DSMB meeting of March 3, 2003, the committee unexpectedly unblinded itself for a second look at the second interim analysis results, and it was concluded that the treatment difference was small but favorable for BiDil. During this meeting, the committee recommended an increase in the sample size.

The fourth DSMB meeting of March 13, 2004, at this meeting the committee formally unblinded itself, reviewed the third interim analysis results and noted that the mortality trend was getting stronger. The DSMB recommended another safety interim analysis in mid summer of 2004 to review mortality data again, and decided to establish monitoring boundaries for mortality since this was not determined early in the trial. The O'Brien-Fleming type group sequential boundary using the Lan-DeMets alpha spending function was chosen to be constructed for 5 interim analyses including the two that were to take place later on. The spending computation showed that the logrank test comparison of treatment groups

fell just below the O'Brien-Fleming boundary value. An estimate of when the logrank z statistic or nominal p-value would cross the boundary values was generated and these were 2.24 for the logrank z statistic and 0.0126 for the p-value. These triggered a discussion by the DSMB about early termination of the trial.

In the meeting of June 9, 2004 with mortality data available on 1014 patients, it was noted that and the trend of mortality strongly favoring the active treatment over the placebo group had continued. The boundary for this analysis was crossed with a longrank z statistic of 2.47 and a logrank two-sided p-value of 0.0132 (less than the required nominal p-value for the interim analysis). The committee recommended that the A-HeFT trial be terminated due to a statistically significant favorable mortality benefit on treatment when compared to control.

5.1.11.1.2 Statistical Issues

The statistical analysis plan was modified as a result of early termination of the trial and most of the changes concerned the way missing data were to be handled, see 5.1.8.5 page 24. For detailed description of the statistical method and changes, refer to Dr. Hung's review.

5.1.11.1.3 Protocol Violations

A total of 216 (20.6%) patients had deviations related to inclusion and exclusion criteria. with similar proportions on both BiDil and placebo.

The majority, ten percent and a half in each group, violated the LV dysfunction criteria. More subjects on BiDil had one or more of the conditions that were to be excluded compared to placebo, 2.1% (11) vs. 1.1% (6) respectively. Similar proportions on both treatment arms were exposed to forbidden medications during the trial, see Table 7 page 28.

5.1.11.2 Patient Disposition

5.1.11.2.1 A-HeFT

Table 6. A-HeFT Patient disposition (primary analysis population)

	BiDil (N=518) n (%)	Placebo (N=532) n (%)
Number of patients randomized	518	532
Completers	469 (91%)	457 (86%)
discontinued study drug prematurely	153 (30%)	101 (19%)
Withdrawal for adverse events	109 (21.1)	63 (12.0)
Discontinued from study prematurely	49 (9%)	75 (14%)
Investigator decision	9 (2%)	13 (2%)
Patient withdrew consent	5 (1%)	3 (1%)
Lost to follow-up	2 (0%)	0 (0%)
Cardiac transplantation	3 (1%)	3 (1%)
Death	30 (6%)	54 (10%)
Not reported	0	2 (0%)
Final status for assessment of the composite endpoint		
Vital status known at study completion	518 (100%)	532 (100%)
Hospitalization status known at study completion	505 (98%)	521 (98%)
QOL assessment done at or before six-month visit	472 (91%)	497 (93%)

Source: Sponsor's report;
[1] Two deaths occurred after completion of patient participation in the study and were not captured on the Study Completion CRF and thus are not captured in this table (112-001 and 231-002).

Very few people were lost to follow-up. Nine more percents of the subjects on BiDil discontinued as a result of adverse events, while 5% more of the subjects on placebo withdrew from the study prematurely.

Table 7. Protocol violations

	BiDil (N=518	Placebo (N=532
Number took prohibited medication	71 (14%)	90 (17%)
Hydralazine	14 (3%)	15 (3%)
Long-acting nitrate	65 (13%)	78 (15%)
Phosphodiesterase-5 inhibitor	3 (1%)	4 (1%)

5.1.11.2.2 V-HeFT

Table 8. Patient disposition in V-HeFT I (Sponsor's analysis)

	HYD/ISDN	Placebo	All
Randomized	186	273	642
Completed	92	134	
Deaths	72	120	283
Discontinuations	22	19	

Table 9. Patient disposition in V-HeFT II

	HYD/ISDN	Enalapril	All
Randomized	401	403	
Completed	199 (49.6)	233 (57.8)	432
Deaths	153 (38.2)	132 (32.8)	285
Discontinuations	49 (12.2)	38 (9.4)	87

5.1.11.3 Demographics

5.1.11.3.1 A-HeFT

Table 10. Baseline demographic, medical and therapeutic characteristics of the A-HeFT population (Dr. Hung's analysis)

Characteristics	Look 2 cohort		Post-look 2 cohort		Entire population	
	BiDil (N=164)	Placebo (N=152)	BiDil (N=354)	Placebo (N=380)	BiDil (N=518)	Placebo (N=532)
Gender						
Male	59.2%	66.5%	54.5%	62.9%	56.0%	63.9%
Female	40.8%	33.5%	45.5%	37.1%	44.0%	36.1%
Age (mean ± sd)	56±12	56±14	57±13	57±13	57±13	57±13
< 65	73.2%	74.3%	68.4%	70.3%	69.9%	71.4%
≥ 65	26.8%	25.7%	31.6%	29.7%	30.1%	28.6%
Weight (kg)	91±27	94±25	92±25	94±26	92±26	94±25
Blood pressure						
Systolic	126±20	121±26	128±18	125±22	128±19	124±24
Diastolic	76±19	71±24	77±11	75±14	77±14	74±17
Heart rate	75±12	72±18	74±11	75±11	74±11	74±14
EF (%)	23.6±7.2	23.8±7.3	24.1±7.4	24.3±7.6	23.9±7.3	24.2±7.5
Hypertension	86.0%	86.8%	93.5%	88.4%	91.1%	88.0%

Characteristics	Look 2 cohort		Post-look 2 cohort		Entire population	
	BiDil (N=164)	Placebo (N=152)	BiDil (N=354)	Placebo (N=380)	BiDil (N=518)	Placebo (N=532)
Arrhythmias	33.5%	35.5%	32.2%	34.2%	32.6%	34.6%
Diabetes Mellitus	40.2%	36.2%	46.9%	37.4%	44.8%	37.0%
Hyperlipidemia	45.7%	41.5%	60.5%	52.6%	55.8%	49.4%
Cerebrovascular disease	17.7%	17.1%	14.1%	12.6%	15.3%	13.9%
Peripheral vascular disease	12.8%	13.2%	10.5%	13.4%	11.2%	13.4%
COPD	20.1%	25.7%	16.4%	18.7%	17.6%	20.7%
Chronic renal insufficiency	15.9%	18.4%	16.4%	18.2%	16.2%	18.2%
Valvular disease	29.3%	30.3%	39.0%	39.0%	35.9%	36.5%
Previous implantable pacemaker or ICD	14.6%	14.5%	17.5%	18.4%	16.6%	17.3%
Previous MI	28.7%	25.7%	29.7%	29.7%	29.3%	28.6%
Angina	0.6%	0.0%	0.6%	0.3%	0.6%	0.2%
Unstable angina in the past 3 months	0.0%	0.0%	0.3%	0.0%	0.2%	0.0%
Cigarette smoking during the past year	31.7%	25.7%	25.7%	26.6%	27.6%	26.3%
Previous cigarette smoking	62.8%	66.5%	57.1%	61.8%	58.9%	63.2%
Stroke	11.0%	11.2%	11.3%	10.0%	11.2%	10.3%
Atrial Fibrillation	18.9%	19.7%	13.8%	16.8%	15.4%	17.7%
TIA	6.7%	6.6%	3.4%	3.4%	4.4%	4.3%
Etiology of HF						
Ischemic	22.6%	22.4%	23.7%	22.9%	23.4%	22.7%
Idiopathic	25.0%	29.0%	24.3%	27.1%	24.5%	27.6%
Hypertensive	39.0%	36.2%	40.4%	37.9%	40.0%	37.4%
Valvular	3.7%	4.0%	2.0%	2.9%	2.5%	3.2%
others	9.8%	8.6%	9.6%	9.2%	9.7%	9.0%
Dyspnea						
Mild	25.6%	30.3%	26.8%	30.0%	26.5%	30.1%
Moderate	64.0%	57.2%	62.2%	55.5%	62.7%	56.0%
Severe	7.3%	7.9%	5.4%	8.4%	6.0%	8.3%
None	3.1%	4.6%	5.7%	6.1%	4.8%	5.6%
Orthopnea						
Mild	24.4%	32.9%	32.8%	34.5%	30.1%	34.0%
Moderate	37.2%	38.2%	38.1%	35.8%	37.8%	36.5%
Severe	11.6%	9.2%	7.3%	6.1%	8.7%	7.0%
None	26.8%	19.7%	21.5%	23.7%	23.2%	22.6%
Fatigue						
Mild	26.2%	23.0%	27.4%	29.8%	27.0%	27.8%
Moderate	61.6%	61.2%	57.6%	53.4%	58.9%	55.6%
Severe	8.5%	12.5%	11.0%	11.8%	10.2%	12.0%
None	3.1%	3.3%	4.0%	5.0%	3.7%	4.5%
Hospitalized in the past year for HF	92.7%	96.7%	61.3%	67.6%	71.2%	75.9%
NYHA class						
I	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
II	0.6%	0.0%	0.0%	0.0%	0.2%	0.0%
III	95.7%	92.8%	97.2%	95.5%	96.7%	94.7%
IV	3.7%	7.2%	2.8%	4.5%	3.1%	5.3%
ACE	79.9%	77.0%	72.0%	74.5%	74.5%	75.2%

Characteristics	Look 2 cohort		Post-look 2 cohort		Entire population	
	BiDil (N=164)	Placebo (N=152)	BiDil (N=354)	Placebo (N=380)	BiDil (N=518)	Placebo (N=532)
ARB	14.6%	16.5%	28.3%	22.9%	23.9%	21.1%
Beta blockers	76.2%	76.3%	87.3%	84.5%	83.8%	82.1%
Calcium blockers	18.3%	17.1%	22.3%	20.5%	21.0%	19.6%
Non-aldosterone antagonist diuretics	91.5%	95.4%	91.2%	91.8%	91.3%	92.9%
Aldosterone antagonist	40.2%	33.6%	40.1%	39.5%	40.2%	37.8%
Digitalis glycosides	70.1%	73.7%	53.4%	55.8%	58.7%	60.9%
Insulin					97 (18.7)*	67 (12.6)
Oral hypoglycemic drugs					156 (30.1)*	119 (22.4)
Potassium supplement					256 (49.4)	271 (50.9)

* $p < 0.05$

As can be seen from the table above, there were more males on placebo.

There were more diabetic patients on BiDil which explains the excess of diabetic drugs in this treatment group.

BiDil subjects had on average higher systolic and diastolic blood pressure;

Subjects on BiDil were more likely to be hypertensive;

Hypertensive as an etiology of HF was more prevalent on BiDil;.

5.1.11.3.2 V-HeFT

Table 11. Demographics and other baseline characteristics of the V-HeFT I population

Characteristics	HYD/ISDN	Placebo
Age (yr.)	58.3	58.5
Heart Failure Symptoms (%)		
< 6 mo.	18.9	19.5
6 mo. – 1.5 yr.	23.2	27.2
1.5 – 4.0 yr.	25.4	22.4
> 4 yr.	32.4	30.9
Race (%)		
White	71	70
Black	27	29
Other	2	1
Etiology		
CAD	44.1	44.3
Previous MI	40.3	42.3
Alcohol excess	43.0	38.2
Hypertension	39.7	42.6
Diabetes	17.2	24.5
Previous Surgery		
Coronary Bypass	11.8	13.6
Valve Replacement	4.9	4.0

Characteristics	HYD/ISDN	Placebo
Previous Therapy*(%)		
Vasodilators	41.9	36.3
Antiarrhythmics	27.4	26.7
Sublingual Nitroglycerin	20.4	19.5
Anticoagulants	17.7	17.6
Clinical data		
Symptom Score	5.6	5.6
Arterial Pressure (mmHg)	119.6/75.0	118.9/76.1
Heart Rate (beats/min.)	83.1	81.5
Cardiothoracic Ratio (%)	52.8	52.9
EF (%)	30.3	30.4
LVIDD (cm/m2)	3.5	3.5
Exercise Duration (min.)	9.7	9.8
Oxygen Consumption (ml/kg/min.)	14.4	15.0

*Previous 6 months;

Table 12. Demographics and other baseline characteristics of the V-HeFT II population

Characteristics	HYD/ISDN N = 401	Enalapril N = 403
Age		
Mean (SD)	60.55 (8.52)	60.62 (8.25)
Race		
White	282 (70.32)	292 (72.46)
Black	109 (27.18)	106 (26.30)
Other	10 (2.29)	5 (1.24)
Duration of CHF (months)		
N	387	383
Mean (SD)	40.15 (48.64)	31.20 (37.84)
NYHA class		
I	22 (5.49)	24 (5.96)
II	210 (52.37)	200 (49.63)
III	167 (41.65)	178 (44.17)
IV	2 (0.50)	1 (0.25)
CAD	213 (53.25)	220 (54.59)
Previous MI	189 (47.13)	197 (48.88)
CVA (n, %)	38 (9.48)	46 (11.41)
Coronary Bypass Surgery	87 (21.70)	85 (21.09)
Hypertension (n, %)	182 (45.39)	199 (49.62)
Diabetes	80 (19.95)	84 (20.84)
Excessive use of alcohol	147 (36.65)	135 (33.50)
Tobacco Use (n, %)	132 (32.92)	135 (33.50)
Previous Therapy*(%)		
Vasodilators	247 (61.60)	250 (62.03)
Antiarrhythmics	106 (26.43)	100 (24.81)
Sublingual Nitroglycerin	67 (16.71)	64 (15.88)
Anticoagulants	88 (21.95)	84 (20.84)
Clinical Assessment		
Arterial Pressure (mmHg)		
Mean systolic/diastolic	126.98/78.44	125.53/77.97
EF (%)		
Mean (SD)	29.42 (11.53)	28.61 (10.87)
Oxygen consumption (ml/kg/min)		
Mean (SD)	13.54 (3.52)	13.84 (3.46)

Characteristics	HYD/ISDN N = 401	Enalapril N = 403
Heart Rate (beats/min.) Mean (SD)	77.25 (11.93)	78.35 (12.06)
Cardiothoracic Ratio (%) Mean (SD)	53.0 (6.2)	53.7 (6.0)
LVIDD (cm/m^2) Mean (SD)	3.23 (1.22)	3.58 (1.42)
Plasma Norepinephrine (pg/ml) Mean (SD)	543. 79 (226.78)	592.59 (388.12)
Plasma rennin activity (ng/ml/hr) Mean (SD)	15.65 (28.09)	19.86 (52.64)
Atrial fibrillation (n, %)	63 (15.71)	46 (11.41)
S, Gallop (n, %)	69 (17.21)	89 (17.21)

5.1.11.4 Efficacy Findings

5.1.11.4.1 A-HeFT

5.1.11.4.1.1 Primary Efficacy Endpoint

5.1.11.4.1.1.1 Composite Score of All-Cause Mortality, First Hospitalization for HF and QOL

Table 13. Scoring of the components of the primary endpoint

Component	Score	BiDil (N = 518) n (%)	Placebo (N = 532) n (%)
Death			
Yes	-3	32 (6.2)	54 (10.2)
No	0	486 (93.8)	478 (89.8)
Missing	-3	0 (0.0)	0 (0.0)
First hospitalization for heart failure			
Yes	-1	85 (16.4)	130 (24.4)
No	0	420 (81.1)	391 (73.5)
Missing	-1	13 (2.5)	11 (2.1)
Change from baseline in QOL at 6 months			
Improvement ≥10 units	2	180 (38.1)	166 (33.4)
Improvement ≥5 and <10 units	1	49 (10.4)	56 (11.3)
Change <5 units	0	117 (22.6)	126 (23.7)
Worsening ≥5 and <10 units	-1	46 (8.9)	32 (6.4)
Worsening ≥10 units	-2	80 (16.9)	117 (23.5)
Missing	-2	46 (8.9)	35 (6.6)

Table 14. Mean change in composite score of Mortality, Hospitalization for HF, and QOL

Composite score	BiDil (N = 518)	Placebo (N = 532)	p-value
Mean change	-0.16	-0.47	0.011[1] 0.016[2] 0.021[3]

Composite score	BiDil (N = 518)	Placebo (N = 532)	p-value
Median	0	0	
Range	-6 to 2	-6 to 2	

[1] unadjusted two-sample t test
[2] sponsor's calculation using adaptive two-sample t test of Cui, Hung and Wang incorrectly
[3] Dr. Hung's calculation using adaptive two-sample t test of Cui, Hung and Wang

Table 15. Mean change in composite score before and after sample size re-estimation at the 2d interim analysis (analyses completed by Dr. Hung)

	Look-2 cohort			post Look-2 cohort		
	BiDil (N=164)	Placebo (N=152)	Difference (B – P)	BiDil (N=354)	Placebo (N=380)	Difference (B – P)
Composite score	-0.23	-0.47	0.24	-0.07	-0.38	0.31

5.1.11.4.1.2 Secondary Efficacy Endpoints

5.1.11.4.1.2.1 Individual Scores of the Components of the Primary Composite

Table 16. Change in the mean of individual scores of the components of the composite endpoint (Sponsor's and Dr. Hung's analyses)

	BiDil (N=518)	Placebo (N=432)	p-value[1]
Death	-0.19	-0.30	0.019
First hospitalization for heart failure	-0.19	-0.27	0.003
Change from baseline in QOL at 6 months	0.21	0.10	0.24

[1] two-sample analysis

As can be seen from the table above, the significant change in the composite score was driven by mortality and hospitalization. The QOL score changed in the right direction but not significantly.

Table 17. Event rate and time to event analysis for deaths and first hospitalization for heart failure (Sponsor's and Dr. Hung's analyses)

	BiDil (N=518)	Placebo (N=432)	Hazard ratio (95% CI)	p-value[1]
Death	32[2] (6.2%)	54 (10.2%)	0.47 (0.37, 0.89)	0.012
First hospitalization for heart failure	86 (18.4%)	130 (24.4%)	0.61 (0.46, 0.80)	< 0.001

[1] Cox regression analysis
[2] Two of these deaths were not included in the sponsor's primary analysis because they occurred one and five days post study closure.

Table 18. Mean change in the composite score at the 2d interim analysis or Look 2 (analyses completed by Dr. Hung)

	Look-2 cohort			post Look-2 cohort		
	BiDil (N=164)	Placebo (N=152)	HR (95% CI)	BiDil (N=354)	Placebo (N=380)	HR (95% CI)
Death	18 (11.0%)	18 (11.8%)	0.93 (0.49, 1.79)	14 (4.0%)	36 (9.5%)	0.38 (0.21, 0.71)

First HF hospitalization	35 (21.3%)	48 (31.6%)	0.66 (0.42, 1.01)	50 (14.1%)	82 (21.6%)	0.58 (0.41, 0.82)

5.1.11.4.1.2.2 Death from Any Cause

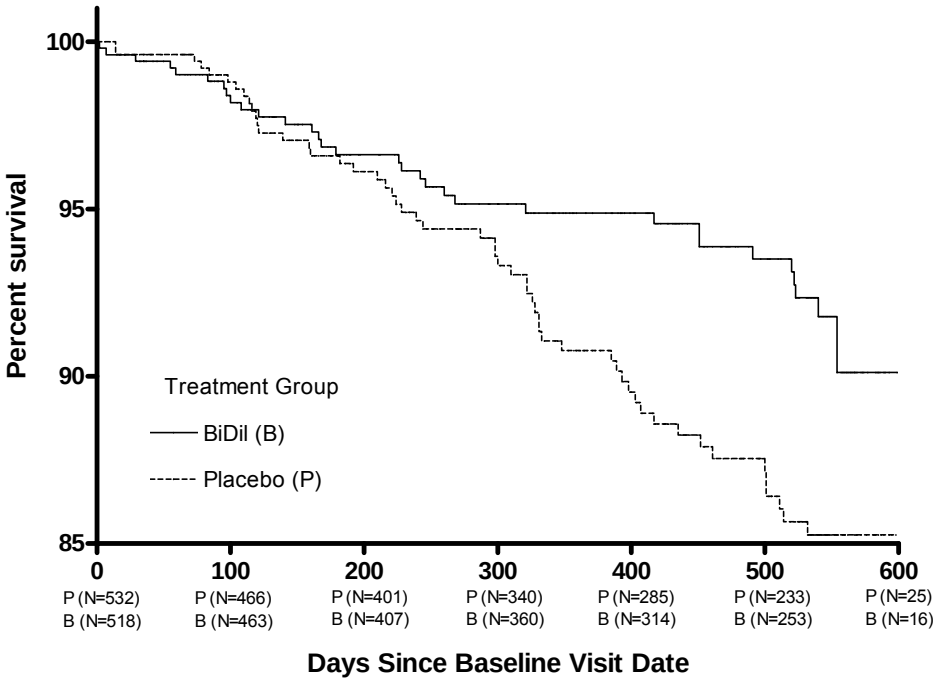
Table 19. Tabulation of causes of death as adjudicated by ICAC (Sponsor's analysis)

	BiDil (N=518)	Placebo (N=532)	Hazard ratio (95% CI)
All-cause mortality	32 (6.2%)	54 (10.2%)	0.47 (0.37, 0.89)
Heart failure deaths	21 (4.1%)	42 (7.9%)	0.61 (0.46, 0.80)
Sudden cardiac death	17 (3.3%)	24 (4.5%)	
Pump failure death	4 (0.8%)	16 (3.0%)	
MI-related death	0 (0.0%)	2 (0.4%)	
Cardiac procedure-related death	0 (0.0%)	0 (0.0%)	
Other cardiac cause-related death	0 (0.0%)	0 (0.0%)	
Non-heart failure (vascular death)	5 (1.0%)	3 (0.6%)	
Cerebrovascular accident death	4 (0.8%)	3 (0.6%)	
Vascular-related death	1 (0.2%)	0 (0.0%)	
Pulmonary embolism-related death	0 (0.0%)	0 (0.0%)	
Other vascular cause-related death	0 (0.0%)	0 (0.0%)	
Non-cardiovascular death	6 (1.2%)	9 (1.7%)	
Non-cardiovascular cause death	3 (0.6%)	5 (0.9%)	
Unknown cause death	3 (0.6%)	4 (0.8%)	

The reduction in all cause mortality was mainly due the reduction in cardiac failure deaths. The risk of sudden death is slightly higher on placebo, but not significantly different.

One case on BiDil and three cases on placebo were classified by the investigator as due to cardiovascular causes, but due to non-cardiovascular causes by the ICAC, Table 49 page 73.

Figure 2. Kaplan-Meier estimates for all-cause mortality by treatment (Sponsor's analysis)



5.1.11.4.1.2.3 Number of Hospitalizations and Total Days in Hospital

Table 20. Hospitalization event rate and total days in hospital (Sponsor's analysis)

	BiDil (N=518)	Placebo (N=532)	p-value
Event rate for hospitalization			
HF hospitalization	85 (16.4%)	130 (24.4%)	< 0.001#
All cause hospitalization	202 (39.0%)	221 (41.5%)	0.41$
Other cardiac cause hospitalization	80 (15.4%)	90 (16.9%)	0.56$
Non-cardiac cause hospitalization	109 (21.0%)	117 (22.0%)	0.76$
Days in hospital (days/patient)			
HF hospitalization			
Mean (SD)	13.7 (16.6)	15.3 (20.2)	0.54*
Range	2 - 122	2 - 164	
All cause hospitalization			
Mean (SD)	13.0 (15.6)	17.7 (21.6)	0.012*
Range	2 - 135	2 - 196	
Other cardiac cause hospitalization			
Mean (SD)	7.2 (10.0)	7.4 (5.7)	0.90*
Range	2 - 84	2 - 26	
Non-cardiac cause hospitalization			
Mean (SD)	8.1 (6.8)	10.6 (11.8)	0.051*
Range	2 - 34	2 - 65	

Table compiled by Dr. Hung

log-rank test $ Fisher's exact test * two-sample t test

Hospitalization for all causes, for other cardiac causes and for non-cardiac causes was not different between the treatment arms.

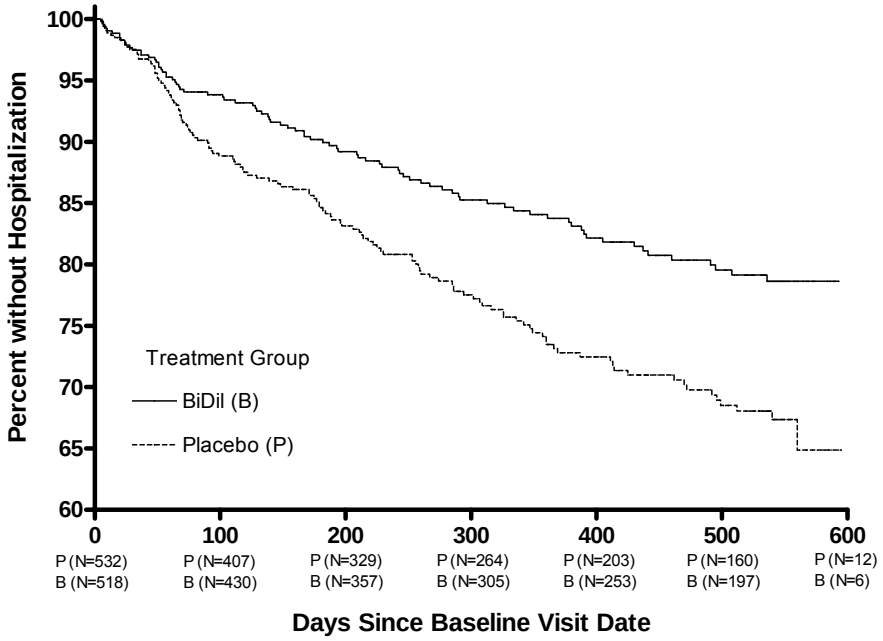
Days in hospital for HF were slightly different between BiDil and placebo, but not statistically significant. This is in contrast of a significant reduction in the rate of first HF hospitalization on BiDil. The lack of a significant difference in days spent in the hospital in the face of a significant difference in the rate of hospitalization for HF could be explained by a competing increased mortality on placebo.

Days in hospital for all causes were significantly reduced on BiDil and days in hospital for non-cardiac causes were of borderline significance.

Table 21. Event rate and time to event analysis for all-cause deaths and hospitalization (post hoc added secondary efficacy analysis)

	BiDil (N=518)	Placebo (N=532)	Hazard ratio (95% CI)	p-value[1]
First hospitalization for heart failure or all-cause mortality	108 (20.8%)	158 (29.7%)	0.63 (0.49, 0.81)	< 0.001
All-cause hospitalization or all-cause mortality	215 (41.5%)	237 (44.5%)	0.86 (0.72, 1.04)	0.12

Figure 3. Kaplan-Meier estimate for first heart failure hospitalization by treatment as adjudicated by the ICAC (Sponsor's analyses)

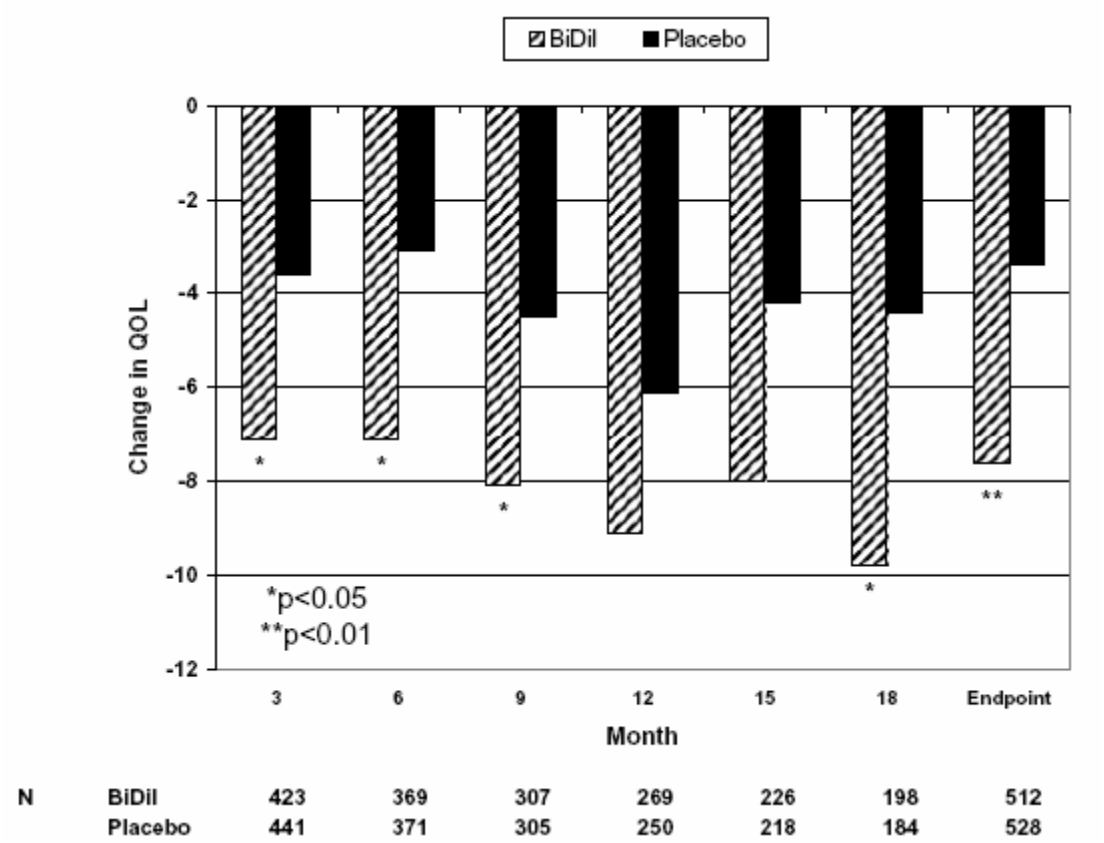


5.1.11.4.1.2.4 Overall Quality Of Life throughout the Trial

Table 22. Quality of Life scores by treatment (Sponsor's analysis)

	BiDil (N=518)	Placebo (N=532)	p-value[1]
Overall score			
Mean baseline	50.9	50.8	
Mean change (SD)	-7.6 (22.6)	-3.4 (22.7)	0.003
Range of change	-91 – 68	-105 – 70	
Physical score			
Mean baseline	22.1	22.0	
Mean change (SD)	-3.5 (10.5)	-1.4 (10.6)	0.002
Range of change	-40 – 29	-401 – 30	
Emotional score			
Mean baseline	10.4	10.4	
Mean change (SD)	-1.3 (6.8)	-0.7 (6.5)	0.13
Range of change	-25 – 22	-25 – 17	

Figure 4. Mean change from baseline in MLHF overall score throughout the trial (Sponsor's analysis)



5.1.11.4.1.2.5 Number of Unscheduled Emergency Room and Office/Clinic Visits

Table 23. Number (%) of patients with unscheduled emergency room or office/clinic visits by cause (Sponsor's analysis)

	BiDil (N = 518) n (%)	Placebo (N = 532) n (%)	p-value[1]
Unscheduled ER visits for any reason			
0	379 (73.2)	385 (72.4)	0.782
1	88 (17.0)	87 (16.4)	
2	27 (5.2)	29 (5.5)	
3	10 (1.9)	17 (3.2)	
≥4	14 (2.7)	14 (2.3)	
Unscheduled ER visits for HF			
0	500 (96.5)	502 (94.4)	0.105
1	14 (2.7)	24 (4.5)	
2	3 (0.6)	2 (0.4)	
3	1 (0.2)	4 (0.8)	
Unscheduled ER visits for other cardiac cause			
0	486 (93.8)	505 (94.9)	0.503
1	27 (5.2)	24 (4.5)	
2	3 (0.6)	2 (0.4)	
3	2 (0.4)	1 (0.2)	
Unscheduled ER visits for non-cardiac cause			
0	401 (77.4)	416 (78.2)	0.767
1	80 (15.4)	77 (14.5)	
2	23 (4.4)	21 (3.9)	
3	7 (1.4)	6 (1.1)	
≥4	7 (1.4)	12 (2.3)	
Unscheduled office/clinic visits for HF			
0	511 (98.6)	528 (99.2)	0.379
1	6 (1.2)	4 (0.8)	
2	0 (0.0)	0 (0.0)	
3	1 (0.2)	0 (0.0)	

[1]Fisher's exact test

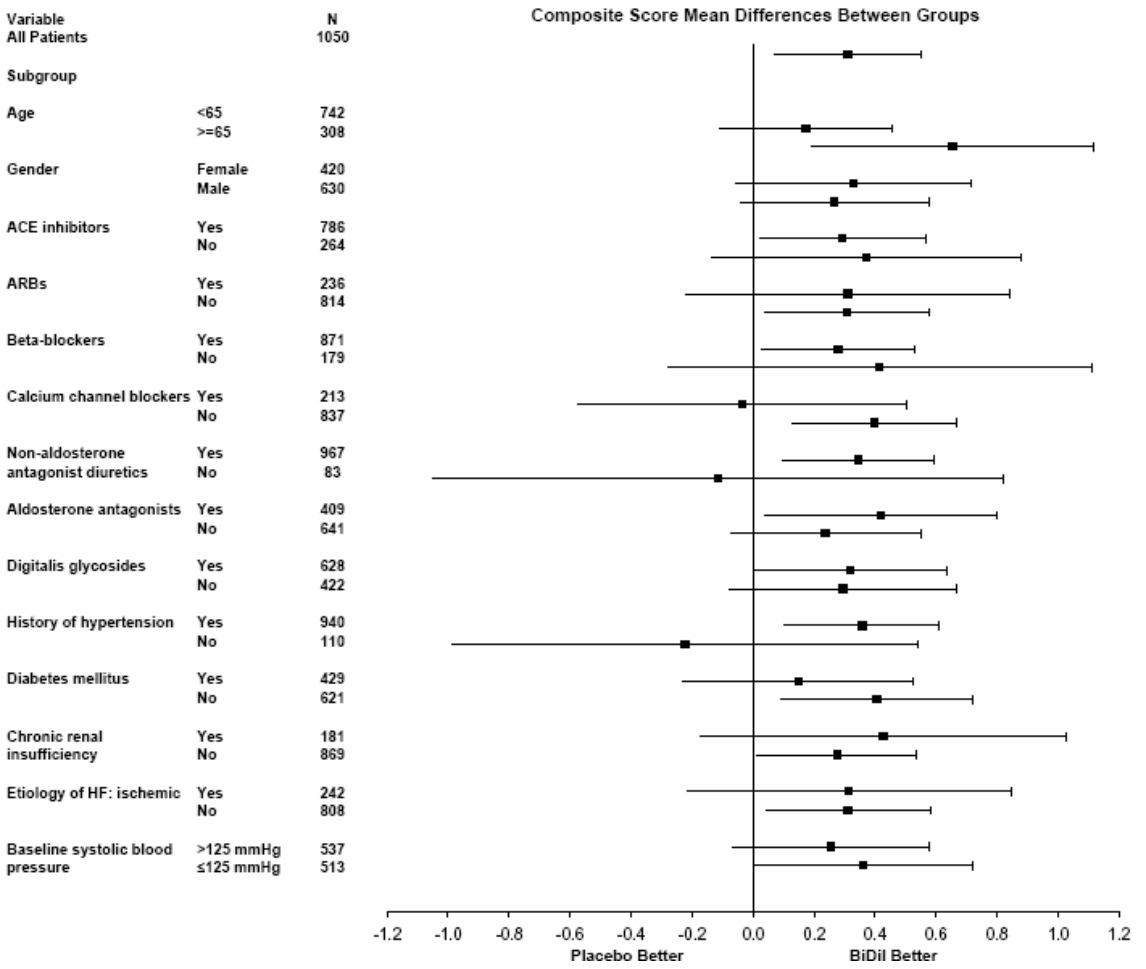
There were no differences between the two treatment groups with regard unscheduled visits for any cause. This may be due to the competing cause of mortality with subjects that would likely have had an unscheduled visit having died.

5.1.11.4.1.2.6 LVEF, LVIDD And LV Wall Thickness

Request to omit these findings from the submission were granted by the Division.

5.1.11.4.1.2.7 Composite Score Mean Differences by Baseline Demographic, Clinical and Therapeutic Characteristics

Figure 5. Composite score mean change by baseline characteristics (Sponsor's analysis)



All subgroup categories seem to have benefited in their score, except for three categories and these are subjects on calcium channel blockers, patients not receiving non-aldosterone antagonist diuretics, and patients with a non-hypertensive etiology of CHF.

5.1.11.4.1.3 Potential Confounding Factors Of Efficacy

Gender -A predominance of males in the placebo group with a difference of 8% between the two groups was observed. Gender being a significant risk factor of cardiovascular disease and death could have put the placebo group at a disadvantage with regard to HF outcomes.

Blood pressure –the BiDil group had higher systolic (+4 mmHg) and diastolic (+3 mmHg) blood pressure readings at baseline. If this difference stemmed from a high prevalence of hypotension in the placebo group this could have put this group at a disadvantage given that hypotension is not a desirable risk factor for HF..

Diabetes mellitus –almost 8% more of the BiDil group had DM at baseline. DM is a significant factor of cardiovascular disease progression and mortality, and it could have put the BiDil group at a disadvantage.

Hyperlipidemia –a little over 5% more of the BiDil group had hyperlipidemia at baseline. Hyperlipidemia a significant risk factor of cardiovascular diseases, and apart from its indirect prediction of the incidence of HF and its progression, it is not known what direct effect this has on the outcome of HF.

Etiology of HF -2.5% more of the placebo group had a non-hypertensive etiology, and 3% more has an idiopathic etiology of HF. The findings of A-HeFT show that BiDil was more effective in the subgroup with a hypertensive etiology.

COPD –a predominance (+3%) of COPD was observed in the placebo group. Given pulmonary edema is a complication of CHF, COPD could have played a role in the deterioration and possibly fatal outcomes of CHF and put the placebo group at a disadvantage.

Other baseline imbalances include 4% more of the placebo patients had a history of previous smoking, 2% more had peripheral vascular disease even if there were less diabetics on placebo, 2% more had arrhythmia, and 2% less each were on concomitant ARBs and aldosterone antagonists known to be beneficial in HF disease.

5.1.11.4.2 V-HeFT

5.1.11.4.2.1 V-HeFT I Efficacy Findings

Table 24. Crude mortality rate and cause of death in the V-HeFT I trial[2]

	BiDil (N = 186)	Placebo (N = 273)	Prazosin (N = 183)
# of deaths	72	120	91
Crude mortality rate	38.7%	44.0 %	49.7%
Cause of death	n (%)	n (%)	n (%)
Pump failure	22 (31)	38 (32)	33 (36)
Primary arrhythmia	27 (37)	45 (38)	32 (35)
Other	6 (8)	4 (3)	6 (7)
Unknown	5 (7)	4 (3)	3 (3)
Cardiac	1 (1)	-	-
Suspected cardiac	10 (14)	20 (17)	-
Not specified	1 (1)	9 (7)	17 (19)

Table 25. Crude mortality and 95% CI for population subgroups[2]

Baseline	BiDil		Placebo		BiDil - Placebo	95% CI
	N	Rate (%)	N	Rate (%)		
CAD						
Yes	82	41.5	121	50.4	-8.9	-22.8, 5.0
No	84	36.5	152	38.8	-2.3	-14.4, 9.8
Race						
Black	49	30.6	79	44.3	-13.7	-30.6, 3.2
Non-black	136	41.9	194	43.8	-1.9	-12.7, 8.9
Baseline EF						

[2] Dr. Hung's review of V-HeFT I

Baseline	BiDil		Placebo		BiDil - Placebo	95% CI
	N	Rate (%)	N	Rate (%)		
> median	88	29.5	123	33.3	-3.8	-16.5, 8.9
< median	88	48.9	131	51.9	-3.0	-16.5, 10.5
Baseline Max O_2						
> median	93	33.3	139	32.4	-1.0	-11.3, 13.3
< median	92	44.6	133	55.6	-11.1	-24.3, 2.1

5.1.11.4.2.2 V-HeFT II Efficacy Findings

Table 26. Crude mortality rate in the V-HeFT II Trial[3]

Crude mortality	BiDil N = 401 n (%)	Enalapril N = 403 n (%)
2-year mortality	95 (23.7)	68 (16.9)
5-year mortality	153 (38.2)	132 (32.8)

Table 27. Cumulative mortality from Life Table Analysis[3]

	Number alive at start		Cumulative mortality (%)	
Year	BiDil	Enalapril	BiDil	Enalapril
1	401	4.3	13.0	09.0
2	329	344	25.0	18.0
3	239	262	36.0	31.0
4	152	165	47.0	42.0
5	84	85	54.0	48.0

p (logrank for survival) 0.019 (2 years), 0.083 (overall)

Table 28. Crude mortality rates based on race and alcohol use[3]

	N	BiDil: Enalapril	BiDil - Enalapril	95% CI	95% CI Hazard Ratio
Black	109	0.36 : 0.37	-0.010	-0.14, 0.12	0.65, 1.58
Non-black	292	0.39 : 0.31	0.077	0.00, 0.15	1.01, 1.74
Alcohol use	147	0.37 : 0.39	-0.011	-0.12, 0.10	0.78, 1.66
No alcohol use	254	0.39 : 0.30	0.087	0.01, 0.17	0.97, 1.75

5.1.11.4.2.3 V-HeFT Trial Analyses Findings by Race

Post-hoc analyses of the V-HeFT I and V-HeFT II study data were used to promote the benefit of BiDil in African-American CHF patients. See Table 2 and Table 3 in 2.1, page 13.

5.1.11.4.3 Efficacy Conclusions

In the pivotal trial, the primary composite endpoint score was shown to be statistically significantly different between the BiDil and placebo treatment arms. The effect on all-cause mortality and first hospitalization for heart failure, two components of the composite endpoint, was shown to be substantial and statistically significant. The score of the third component of this composite, the QOL was shown not to be statistically significantly different between the treatment arms, but a trend of an effect was observed. This does not carry as much weight because it is not as robust in predicting the progression of HF as the other two components of the primary endpoint.

[3] Dr. Hung's review of V-HeFT II

From the supportive trials in the overall study populations, the difference in mortality rates was either not statistically significant when BiDil was compared to placebo (V-HeFT I), Table 24, page 41, or it was higher on BiDil compared to enalapril (V-HeFT II), Table 26, page 42 and Table 27, page 42. Subgroup analyses have shown that crude mortality rates in Blacks on BiDil were either substantially reduced compared to placebo (V-HeFT I), Table 25 page 41, or trending toward a reduction compared to enalapril, Table 28 page 42.

5.1.11.4.3.1 Could Lowering Blood Pressure Have Accounted for the Difference Observed in Effect?

Blood pressure on BiDil was consistently and statistically significantly reduced at all visits including the 6-month time point; Table 42, page 57.

Additionally, subgroup analysis showed that BiDil had more effect in subjects with a history of hypertension than those without, Figure 5 page 40.

In the V-HeFT II trial, systolic and diastolic blood pressure on enalapril decreased to a greater degree compared to BiDil (-3-4 mmHg vs. -1-1.5 mmHg) at 12 months.

A meta-analysis investigating whether pharmacological properties of antihypertensive drugs or reduction of systolic pressure accounted for cardiovascular outcome in hypertensive or high-risk patients was conducted[4]. The authors' conclusion was that the effect of anti-hypertensive drugs, ACE inhibitors and betablockers had an effect on the prognosis of cardiovascular diseases through their anti-hypertensive effects. [5]

5.1.11.4.3.2 The Effect Of Other Covariates

Analyses conducted by Dr. Hung adjusting for baseline characteristics (discussed in 5.1.11.4.3.2 page 43) that are believed to be associated with HF outcomes, did not change the magnitude or the significance of the effect of BiDil on the primary endpoint.

5.1.11.4.3.3 Is It a Difference of Race?

To think in terms of a difference in effect of a biopharmaceutical substance one can't help thinking in terms of a difference in the pathophysiology of the condition intended for treatment. This was the hypothesis that the Sponsor put forward to explain the failure of the V-HeFT trials in demonstrating the effect of BiDil in a population that was predominantly Caucasian, the V-HeFT post-hoc analysis findings by race, and the success of A-HeFT in preventing undesirable HF outcomes in an African-American population.

What is problematic in relating the effect observed in A-HeFT to race and interpreting it at the pathophisiological or molecular level is the definition used, an old-fashioned way of determining race which relies one's perception of one's race.

The difference by race in the response of hypertension to ACE inhibitors was determined as a result of consistent findings from many ACE inhibitors hypertension trials even though a difference in response at the physiological level was demonstrated only in small numbers of patients and using only surrogate markers.

---

[4] Staessen, JA, Wang JG, Thijs L, Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001; 358: 1305-15

[5] Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13

Given that Caucasians respond favorably to ACE inhibitors for the treatment of both hypertension and heart failure and that AA do not respond well to ACE inhibitors for the treatment of hypertension, one would expect that AA would not respond well to ACE inhibitors for the treatment of heart failure either.

Hypertension is a well-established determinant of incident heart failure and of its prognosis. Racial differences in patients with heart failure were reported to be in the mean age, prevalence of hypertension, left ventricular hypertrophy and ejection fraction. It is also reported that hypertension is more prevalent as an etiologic factor of HF in African Americans than in Caucasians. The characteristics (cited above) of the average African American failing heart are telling of a prevalent pathophysiology of systemic resistance as a cause of and/or a precipitating factor of HF. Common sense dictates that the reduction of this resistance would not only prevent HF, but its deleterious outcomes as well.

The reviewer's argument is that finally a drug is probably able to efficiently control blood pressure in AAs and prevent the consequences of both hypertension and HF. Facts that support and those that do not support the reviewer's argument follow:

--Facts NOT supporting:

-Lack of data that the HYD/ISDN combination is effective in the treatment of hypertension in AAs;

-Lack of data that the combination is superior to ACE-Is, ARBs and/or beta-blockers in the treatment of hypertension in AAs;

-Lack of data from well-conducted clinical trials that lowering BP is the mechanism by which the above therapies reduce and/or delay the outcomes of HF;

--Facts supporting:

-Anti-hypertensive therapies are well documented therapies for HF;

-Most medications that were shown to be effective in HF including ACE-Is, beta-blockers, ARBs, aldosterone antagonists and now BiDil have a strong feature in common, lowering blood pressure;

-Findings of the V-HeFT trials: in the V-HeFT I, BiDil seems[6] to be superior to placebo in AAs, and in the V-HeFT II, BiDil seems to be "non-inferior"[7] to enalapril in AA patients, especially that enalapril was shown to be clearly superior to BiDil in the overall population;

-In A-HeFT:

-the group of patients on BiDil had a higher prevalence of hypertension at baseline and a higher prevalence of hypertension as an etiologic factor of HF;

-the mean BP at baseline of the subjects on BiDil was higher than that of subjects on placebo;

[6] the term "seem" is used because the analyses were not pre-specified, and the findings are result of post-hoc analysis

[7] the design was not a non-inferiority design, but the trend was shifted toward no difference between AA on BiDil and AA on enalapril

-the mean change from baseline in trough blood was significantly greater on BiDil compared to placebo;

-In V-HeFT II enalapril lowered BP to a greater extent than BiDil;

-Data from two meta-analyses concluding that lowering blood pressure in HF wards off its undesirable outcomes (see selected figures from these publications: Figure 6 page, Figure 7 page 83, Figure 8 page 84 and Figure 9 page 85):

· Staessen, JA, Wang JG, Thijs L, Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001; 358: 1305-15.

· Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13

6 INTEGRATED REVIEW OF SAFETY

6.1 Methods and Findings

In the pivotal trial, assessment of safety was to consist of monitoring and recording all adverse events, SAEs, measurements of vital signs, and findings of physical examinations.

It was assumed that the safety profile of BiDil was known, therefore, there was to be no routine laboratory monitoring. Abnormal laboratory values or test results were considered as adverse events only if they induced clinical signs or symptoms or required change in therapy.

Hospitalization for HF, worsening of HF, and unscheduled office or emergency room visits for HF were not to be reported as adverse events because they were to be assessed as efficacy endpoints.

An independent Data and Safety Monitoring Board was to monitor the conduct of the study, review periodic reports of safety data by blinded treatment group, and make recommendations to the Steering Committee.

In addition, data from the V-HeFT I and V-HeFT II studies and from the CB-01 and CB-02 were reviewed for safety.

CB-01 "The 36-Hour Relative Bioavailability of BiDil, a Fixed Combination of Hydralazine/Isosorbide dinitrate, compared to Equivalent Doses of Reference Products (Pilot Study)". In this study 12 subjects received one dose of BiDil.

CB-02 "The Relative Bioavailability of Low and High dose BiDil, a fixed combination of Hydralazine HCL and isosorbide dinitrate, compared to an Oral Solution, Tablet, and Capsule of Hydralazine HCL and ISDN (Pivotal Bioequivalence Study)"

6.1.1 Overview of Adverse Events

Table 29. Summary of overall adverse events (Sponsor's summary)

	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Patients with at least one adverse event	475 (91.9)	432 (82.0)
Patients with at least one drug-related adverse event[1]	350 (67.7)	167 (31.7)

	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Patients with at least one serious adverse event[2]	181 (35.0)	183 (34.7)
Patients with at least one drug-related serious adverse event [1, 2]	13 (2.5)	15 (2.8)
Patients who died[3]	32 (6.2)	54 (10.2)
Patients who permanently discontinued study drug due to adverse events[4]	109 (21.1)	63 (12.0)

[1] Assessed by the investigator as being possibly, probably, or definitely related to study drug.
[2] Serious adverse events exclude clinical endpoint HF hospitalization and adverse event death.
[3] Adjudicated by the ICAC includes two patients (112-001 and 231-002) who died post-study.
[4] As recorded on the adverse event CRF, includes patients who completed the study and those who did not complete the study, may include patients who temporarily stopped study drug as well as permanent discontinuations.

6.1.2 Deaths

Deaths are summarized under the efficacy section because all cause mortality is a component of the primary endpoint and stands on its own as a secondary endpoint.

6.1.3 Other Serious Adverse Events

6.1.3.1 Serious Adverse Events that led to Discontinuation

Table 30. Serious adverse events that led to discontinuation, overall incidence

AE leading to discontinuation[1]	BiDil N = 517 n (%)	Placebo N = 527 n (%)	AE leading to discontinuation[1]	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Any AE N (%)	29 (5.6)	32 (6.1)			
Chest pain	3 (0.6)	1 (0.2)	CVA	1 (0.2)	3 (0.6)
Heart arrest	3 (0.6)	3 (0.6)	Syncope	1 (0.2)	0.0
Heart failure	3 (0.6)	4 (0.8)	Gastroenteritis	1 (0.2)	1 (0.2)
Hypotension	3 (0.6)	1 (0.2)	Myasthenia	1 (0.2)	0.0
Kidney failure	3 (0.6)	1 (0.2)	Dyspnea	1 (0.2)	2 (0.4)
Infection	2 (0.4)	0.0	Edema of the lung	1 (0.2)	0.0
Ventricular fibrillation	2 (0.4)	0.0	Angioedema	1 (0.2)	0.0
Dizziness	2 (0.4)	0.0	Carcinoma of the breast	1 (0.2)	0.0
Arrhythmia	1 (0.2)	0.0	Uremia	1 (0.2)	0.0

As can be seen from the table above, the numbers are very small but more events, the ones expected to be observed, on BiDil were serious and led to discontinuation including hypotension, dizziness and chest pain. Of note are 3 cases of kidney failure vs. 1, and 2 cases of ventricular fibrillation vs. none on BiDil and placebo respectively.

6.1.3.2 Serious Adverse Events

Table 31. Serious adverse events, overall incidence

SAEs	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR
Number (%) of patients with at least one SAE	181 (35.0)	183 (34.7)	1.0
Chest pain	33 (6.4)	29 (5.5)	1.2
Heart failure	16 (3.1)	41 (7.8)	0.4
Ventricular tachycardia	14 (2.7)	8 (1.5)	1.8
Pneumonia	12 (2.3)	8 (1.5)	1.5
Syncope	11 (2.1)	8 (1.5)	1.4
Dyspnea	10 (1.9)	12 (2.3)	0.8
Arrhythmia	9 (1.7)	7 (1.3)	1.3
Hypotension	8 (1.5)	3 (0.6)	2.5
Heart arrest	7 (1.4)	9 (1.7)	0.8
CVA	7 (1.4)	13 (2.5)	0.6
Dizziness	7 (1.4)	0.0	NA
Cellulites	6 (1.2)	2 (0.4)	3.0
DM	6 (1.2)	5 (0.9)	1.3
Cerebral ischemia	5 (1.0)	1 (0.2)	5.0
Coronary artery disease	5 (1.0)	2 (0.4)	2.5
Anemia	5 (1.0)	3 (0.6)	1.7
Bronchitis	5 (1.0)	3 (0.6)	1.7
Dehydration	5 (1.0)	4 (0.8)	1.3
Angina pectoris	5 (1.0)	5 (0.9)	1.1
Hyperglycemia	5 (1.0)	5 (0.9)	1.1
Hypoglycemia	5 (1.0)	5 (0.9)	1.1
Infection	5 (1.0)	5 (0.9)	1.1
Acute kidney failure	5 (1.0)	8 (1.5)	0.7
Neoplasm/carcinoma	4 (0.8)	1 (0.2)	4.0
Gout	4 (0.8)	3 (0.6)	1.3
Atrial fibrillation	4 (0.8)	3 (0.6)	1.3
GI hemorrhage	4 (0.8)	5 (0.9)	0.9
Kidney failure	4 (0.8)	5 (0.9)	0.9
Myocardial infarct	4 (0.8)	9 (1.7)	0.5
Sepsis	3 (0.6)	1 (0.2)	3.0
Asthma	3 (0.6)	2 (0.4)	1.5
Injury, accidental	3 (0.6)	8 (1.5)	0.4
Cholecystitis	3 (0.6)	0.0	NA
Cholelithiasis	3 (0.6)	0.0	NA
Supraventricular tachycardia	3 (0.6)	0.0	NA
Esophagitis	2 (0.4)	1 (0.2)	2.0
Edema of the lung	2 (0.4)	1 (0.2)	2.0
Headache	2 (0.4)	2 (0.4)	1.0
Osteomyelitis	2 (0.4)	2 (0.4)	1.0
Peripheral vascular disease	2 (0.4)	2 (0.4)	1.0
Bradycardia	2 (0.4)	3 (0.6)	0.7
Digitalis intoxication	2 (0.4)	4 (0.8)	0.5
Gastroenteritis	2 (0.4)	4 (0.8)	0.5
Hyperkalemia	2 (0.4)	5 (0.9)	0.4
Hemorrhage, cerebral+	2 (0.4)	0.0	NA

SAEs	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR
subarachnoid			
Thrombophlebitis, deep	2 (0.4)	0.0	NA
Angioedema	2 (0.4)	0.0	NA
Ascites	2 (0.4)	0.0	NA
Infection viral/fungal	2 (0.4)	0.0	NA
Fibrillation, ventricular	2 (0.4)	0.0	NA
Anomaly Vascular	1 (0.2)	1 (0.2)	1.0
Coagulation disorder	1 (0.2)	1 (0.2)	1.0
Creatinine increased	1 (0.2)	1 (0.2)	1.0
Hyponatremia	1 (0.2)	1 (0.2)	1.0
Diarrhea	1 (0.2)	1 (0.2)	1.0
Liver failure	1 (0.2)	1 (0.2)	1.0
Neoplasm of the prostate	1 (0.2)	1 (0.2)	1.0
Myasthenia	1 (0.2)	1 (0.2)	1.0
Palpitations	1 (0.2)	1 (0.2)	1.0
UTI	1 (0.2)	1 (0.2)	1.0
Dyspepsia	1 (0.2)	2 (0.4)	0.5
Kidney function abnormal	1 (0.2)	4 (0.8)	0.3
Anemia, iron deficiency	1 (0.2)	0.0	NA
Alkalosis	1 (0.2)	0.0	NA
Arrhythmia NOD	1 (0.2)	0.0	NA
Arthralgia	1 (0.2)	0.0	NA
Carcinoma of the breast	1 (0.2)	0.0	NA
Hypokalemia	1 (0.2)	0.0	NA
Ketosis	1 (0.2)	0.0	NA
Cerebral infarct	1 (0.2)	0.0	NA
Emotional labiality	1 (0.2)	0.0	NA
Edema of the face	1 (0.2)	0.0	NA
Gastritis, hemorrhagic	1 (0.2)	0.0	NA
Gait abnormal	1 (0.2)	0.0	NA
Hematemesis	1 (0.2)	0.0	NA
Herpes Zoster	1 (0.2)	0.0	NA
Uremia	1 (0.2)	0.0	NA
Leucopenia	1 (0.2)	0.0	NA
Thrombocytopenia	1 (0.2)	0.0	NA
Necrolysis	1 (0.2)	0.0	NA
Ophtalmitis	1 (0.2)	0.0	NA
Parathyroid disease	1 (0.2)	0.0	NA
Respiratory distress	1 (0.2)	0.0	NA
Skin ulcer	1 (0.2)	0.0	NA
Thinking abnormal	1 (0.2)	0.0	NA
Vascular disease	1 (0.2)	0.0	NA
Wrist drop	1 (0.2)	0.0	NA
Gastritis	1 (0.2)(	2 (0.4)	0.5

As can be seen from the table above, some of the adverse events that were expected to be observed were reported as serious in excess on BiDil including hypotension, dizziness and syncope. Other serious adverse events were also reported in excess on BiDil compared to placebo and these are ventricular tachycardia, pneumonia, cellulites, cerebral ischemia, CAD, anemia and bronchitis.

6.1.4 Other Significant Adverse Events

6.1.4.1 Overall Profile of Dropouts

Forty nine (9.5%) of the subjects on BiDil and 75 (14%) of the subjects on placebo discontinued the study prematurely. One hundred and nine (21%) of the subjects on BiDil and 63 (12%) of the placebo patients discontinued the study medication as a result of adverse events. Five BiDil and 3 placebo subjects withdrew consent, 2 BiDil subjects were lost to follow-up, 9 (1.7%) BiDil and 13 (2.4%) placebo patients discontinued per investigator decision, 3 in each study group discontinued for cardiac transplant and 32 BiDil and 54 placebo patients died.

6.1.4.2 Adverse Events Associated with Permanent Discontinuation

Twenty one percent (109) on BiDil and 12% (63) on placebo permanently discontinued the study drug as a result of adverse events. Using the number of events, 5.9% (170 of all events) compared to placebo 3.3% (91 of all events) led to permanent discontinuation.

Table 32. Adverse events leading to treatment discontinuation (number and % of subjects)

AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR	AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR
Any AE N (%)	109 (21.1)	63 (12.0)	1.8				
Asthenia	12 (2.3)	1 (0.2)	11.5	Ventricular fibrillation	2 (0.4)	0.0	NA
Headache	38 (7.4)	4 (0.8)	9.3	Angioedema	1 (0.2)	0.0	NA
Dizziness	19 (3.7)	4 (0.8)	4.6	Amblyopia	1 (0.2)	0.0	NA
Pain	4 (0.8)	1 (0.2)	4.0	Anorexia	1 (0.2)	0.0	NA
Chest pain	8 (1.5)	2 (0.4)	3.8	Neck pain	1 (0.2)	0.0	NA
Nausea	8 (1.5)	2 (0.4)	3.8	Carcinoma	1 (0.2)	0.0	NA
Hypotension	7 (1.4)	3 (0.6)	2.3	Carcinoma of the breast	1 (0.2)	0.0	NA
Abdominal pain	2 (0.4)	1 (0.2)	2.0	Dehydration	1 (0.2)	0.0	NA
Chills	2 (0.4)	1 (0.2)	2.0	Edema of the face	1 (0.2)	0.0	NA
Kidney failure	2 (0.4)	1 (0.2)	2.0	Edema peripheral	1 (0.2)	0.0	NA
Malaise	2 (0.4)	1 (0.2)	2.0	Edema of the lung	1 (0.2)	0.0	NA
Heart arrest	3 (0.6)	3 (0.6)	1.0	Fever	1 (0.2)	0.0	NA
Confusion	2 (0.4)	2 (0.4)	1.0	Hyperglycemia	1 (0.2)	0.0	NA
Diarrhea	2 (0.4)	2 (0.4)	1.0	Hypertension	1 (0.2)	0.0	NA
Gastroenteritis	1 (0.2)	1 (0.2)	1.0	Infection	1 (0.2)	0.0	NA
Back pain	1 (0.2)	1 (0.2)	1.0	Infection fungal	1 (0.2)	0.0	NA
Acute kidney failure	1 (0.2)	1 (0.2)	1.0	Impotence	1 (0.2)	0.0	NA
Myasthenia	1 (0.2)	1 (0.2)	1.0	Ketosis	1 (0.2)	0.0	NA
Nervousness	1 (0.2)	1 (0.2)	1.0	Breast neoplasm	1 (0.2)	0.0	NA
Pruritus	1 (0.2)	1 (0.2)	1.0	Lab tests abnormal	1 (0.2)	0.0	NA
Heart failure	3 (0.6)	4 (0.8)	0.8	Myalgia	1 (0.2)	0.0	NA
Dyspepsia	1 (0.2)	2 (0.4)	0.5	Photophobia	1 (0.2)	0.0	NA
Cerebrovascular accident	1 (0.2)	3 (0.6)	0.3	Pleural effusion	1 (0.2)	0.0	NA
Constipation	1 (0.2)	3 (0.6)	0.3	Somnolence	1 (0.2)	0.0	NA
CVA	1 (0.2)	3 (0.6)	0.3	Sweat	1 (0.2)	0.0	NA
Dyspnea	1 (0.2)	4 (0.8)	0.3	Vasodilatation	1 (0.2)	0.0	NA
Nausea vomiting	3 (0.6)	0.0	NA	Weight decrease	1 (0.2)	0.0	NA
Paresthesia	3 (0.6)	0.0	NA	Uremia	1 (0.2)	0.0	NA
Abnormal kidney function	2 (0.4)	0.0	NA	Hypoglycemia	0.0	2 (0.4)	NA
Kidney function	2 (0.4)	0.0	NA	Myocardial infarction	0.0	4 (0.8)	NA

AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR	AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR
abnormal							
Palpitations	2 (0.4)	0.0	NA	Rash	0.0	3 (0.6)	NA
Syncope	2 (0.4)	0.0	NA	Rectal hemorrhage	0.0	2 (0.4)	NA

Table excludes hospitalization for HF and death. A patient can have more than one event or type of event; each patient is counted only once in each category.

Discontinuation of study drug due to adverse events was observed in excess (80% excess in risk) on BiDil, and headache alone accounted for a third of these. Headache, dizziness, asthenia, chest pain, nausea, and hypotension accounted for 84% of the discontinuations on BiDil and only 25% of the discontinuations on placebo.

Of note are two cases of ventricular fibrillation, and two cases of syncope on BiDil vs. none on placebo.

6.1.4.3 Adverse Events Associated with Temporary Discontinuation or Dose Adjustment

Dose adjustment or temporary study drug discontinuation occurred at a higher incidence in patients on BiDil 42.2% (218) compared to those on placebo 25.2% (133), and of these 19.3% (42) and 26.3% (35) returned to pre-event dose level.

Twenty percent (570) and 13% (341) of the events led to temporary discontinuation or dose level adjustment in BiDil and placebo respectively.

6.1.5 Other Search Strategies

The clinical and statistical results of the V-HeFT studies reported here are those summarized by the Division's review of the original NDA (Doctors Hung, Chen and Ganley, 1997).

6.1.6 Common Adverse Events

6.1.6.1 Eliciting Adverse Events Data in The Development Program

Investigators were instructed to report all adverse events that occur before, during or within 14 days following the cessation of treatment whether or not believed to be related to the study drug. Patients were assessed every three months when they returned for a study visit.

There were no plans to assess of the effect of BiDil on laboratory parameters, QT interval and the immune system because it was assumed that its safety profile was known.

6.1.6.2 Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse events were summarized by body system and using the COSTART preferred term. This categorization and the preferred term used were used in other trials and deemed acceptable.

6.1.6.3 Incidence of Common Adverse Events in the A-Heft Trial

Table 33. Common adverse events, overall incidence by treatment (≥0.4%, and where in excess on BiDil)

	BiDil N = 517 n (%)	Placebo N = 527 n (%)	*RR*		BiDil N = 517 n (%)	Placebo N = 527 n (%)	*RR*
N (%) with at least one AE	475 (91.9)	432 (82.0)	*1.1*				

	BiDil N = 517 n (%)	Placebo N = 527 n (%)	*RR*		BiDil N = 517 n (%)	Placebo N = 527 n (%)	*RR*
Headache	256 (49.5)**	111 (21.1)	*2.3*	Infection, viral	7 (1.4)	3 (0.6)	*2.3*
Dizziness	165 (31.9)**	72 (13.7)	*2.3*	Myalgia	7 (1.4)	3 (0.6)	*2.3*
Asthenia	70 (13.5)	59 (11.2)	*1.2*	Rectal disease	7 (1.4)	4 (0.8)	*1.8*
Nausea	50 (9.7)*	32 (6.1)	*1.6*	Abscess peridontal	6 (1.2)	4 (0.8)	*1.5*
Bronchitis	43 (8.3)	34 (6.5)	*1.3*	Angioedema	6 (1.2)	1 (0.2)	*6.0*
Hypotension	41 (7.9)*	23 (4.4)	*1.8*	Cerebral ischemia + infarct	6 (1.2)	2 (0.4)	*3.0*
Syncope	23 (4.4)	20 (3.8)	*1.2*	Infection, sepsis	6 (1.2)	1 (0.2)	*6.0*
Sinusitis	22 (4.3)*	9 (1.7)	*2.5*	Malaise	6 (1.2)	1 (0.2)	*6.0*
Ventricular tachycardia	21 (4.1)	14 (2.7)	*1.5*	Cardiovascular disease	5 (1.0)	0.0	
GI disorder	20 (3.9)	14 (2.7)	*1.4*	Hernia	5 (1.0)	0.0	
				Melena	5 (1.0)	3 (0.6)	*1.7*
Palpitations	20 (3.9)	14 (2.7)	*1.4*	Tendon disease	5 (1.0)	2 (0.4)	*2.5*
Rhinitis	19 (3.7)	14 (2.7)	*1.3*	Cholelithiasis	4 (0.8)	1 (0.2)	*4.0*
Paresthesia	18 (3.5)	12 (2.3)	*1.5*	Hypotension, postural	4 (0.8)	2 (0.4)	*2.0*
Vomiting	18 (3.5)	10 (1.9)	*1.8*	Respiratory disease	4 (0.8)	2 (0.4)	*2.0*
Amblyopia	16 (3.1)	7 (1.3)	*2.4*	Tachycardia, supraventricular	4 (0.8)	0.0	
Hyperlipidemia	15 (2.9)	10 (1.9)	*1.5*	Vascular, anomaly	4 (0.8)	1 (0.2)	*2.0*
Abnormal kidney function	14 (2.7)	7 (1.3)	*2.1*	Vision abnormal	4 (0.8)	2 (0.4)	*2.0*
Cellulitis	11 (2.1)	9 (1.7)	*1.2*	Photosensitivity	3 (0.6)	1 (0.2)	*3.0*
Tachycardia	11 (2.1)	6 (1.1)	*1.9*	Bone disease	3 (0.6)	1 (0.2)	*3.0*
Infection, fungal	10 (1.9)	6 (1.1)	*1.7*	Duodenitis	3 (0.6)	0.0	
Sweat increase	10 (1.9)	5 (0.9)	*2.1*	Ear disorder	3 (0.6)	0.0	
Fever	9 (1.7)	7 (1.3)	*1.3*	Gastritis, hemorrhagic	3 (0.6)	1 (0.2)	*3.0*
Neoplasm	9 (1.7)	4 (0.8)	*2.1*	Headache, migraine	3 (0.6)	1 (0.2)	*3.0*
Pain, neck	9 (1.7)	7 (1.3)	*1.3*	Hypoxia	3 (0.6)	0.0	
Allergy reaction	9 (1.7)	6 (1.1)	*1.5*	Osteoporosis	3 (0.6)	0.0	
Arthralgia	8 (1.5)	2 (0.4)	*3.8*	Tenosynovitis	3 (0.6)	1 (0.2)	*3.0*
Somnolence	8 (1.5)	2 (0.4)	*3.8*	Vascular disease	3 (0.6)	1 (0.2)	*3.0*
Alopecia	7 (1.4)	3 (0.6)	*2.3*	Hepatomegaly	2 (0.4)	0.0	
Coronary artery disease	7 (1.4)	4 (0.8)	*1.8*	Hydronephrosis	2 (0.4)	0.0	
Cholecystitis	7 (1.4)	0.0		Thrombocytopenia	2 (0.4)	0.0	
Hypercholesterolemia	7 (1.4)	2 (0.4)	*3.5*	Uremia	2 (0.4)	0.0	

A patient can have more than one event or type of event; each patient is counted only once in each category.
***** $p < 0.05$, BiDil vs. placebo
****** $p < 0.0001$, BiDil vs. placebo

There was one case of lupus-like syndrome reported as joint disorder (narrative 9.5, page 75) which resolved after treatment and without a change to the study medication. Also, there was an excess of arthralgia (almost 4 times as frequent) on BiDil compared to placebo.

As can be seen from the table above, the overall rate of adverse events is not very different between the two treatment arms. Headache and dizziness are statistically significantly different between BiDil and placebo. Differences between BiDil and placebo reached statistical significance with regard to hypotension, nausea and sinusitis. Other adverse events where an increase on BiDil was observed include tachycardia, ventricular tachycardia, palpitations and supraventricular tachycardia; GI disorders and vomiting; paresthesia, sweat increase, and amblyopia and abnormal vision; hyperlipidemia and hypercholesterolemia; abnormal kidney

function and uremia;, infections (fungal, viral, sepsis and periodontal abscess); allergy reactions, and angioedema; CVD and cerebral ischemia and/or infarct; arthralgia, malaise, myalgia, tendon disease, and tenosynovitis; hernia; rectal disease and melena; bronchitis, and respiratory disease; cholecystitis and cholelithiasis; somnolence; and neoplasm.

6.1.6.4 Incidence of Common Adverse Events In The V-Heft I And V-Heft II Trials

6.1.6.4.1 Incidence of Adverse Events in Blacks in the V-HeFT Studies

Table 34. Incidence of adverse events in the African-American subpopulation of the V-HeFT trials

Events	BiDil N = 158 n (%)	Placebo N = 79 n (%)	Enalapril N = 106 n (%)
Headache	113 (72%)	43 (54%)	68 (64%)
Dizziness	106 (67%)	42 (53%)	71 (67%)
Arthralgia	103 (65%)	48 (61%)	76 (72%)
Other*	82 (52%)	35 (44%)	63 (59%)
Palpitation	84 (53%)	29 (37%)	52 (49%)
Nausea or Vomiting	75 (47%)	32 (41%)	60 (57%)
Ischemic Chest Pain	58 (37%)	29 (37%)	44 (42%)
Diarrhea	63 (40%)	30 (38%)	46 (43%)
Flushing	50 (32%)	22 (28%)	23 (22%)
Rash	51 (32%)	23 (29%)	37 (35%)
Fever	52 (33%)	17 (22%)	31 (29%)
Syncope	36 (23%)	16 (20%)	16 (15%)

Table from the sponsor's report;

*Was not broken into specific AEs;

6.1.6.4.2 Incidence of Adverse Events in all Patients of the V-HeFT I Study

Six percent (11) and 1% (3) discontinued BiDil and placebo as a result of adverse events.

Table 35. Incidence of adverse events that resulted in dose reduction in V-HeFT I

Adverse Event	HYD/ISDN N = 186 %	Placebo N = 273 %
Any	51.6	22.0
Headache	40.3	5.5
Dizziness	25.8	12.1
Arthralgia	4.8	2.2
Other	11.3	6.6
Palpitations	10.8	2.6
Nausea or vomiting	11.3	5.5
Ischemic chest pain	3.8	2.6
Diarrhea	4.3	1.5
Abdominal pain	7.0	2.9
Flushing	8.6	1.1
Rash	4.3	1.5
Fever	3.8	0.0
Syncope	2.2	4.4

[1] Table from the V-HeFT I Medical/Statistical Review

Table 36. Incidence of adverse events in the V-HeFT I study

Adverse Event	HYD/ISDN N = 186 %	Placebo N = 273 %
Any	94.6	87.2
Headache	74.7	50.9
Dizziness	70.4	59.7
Arthralgia	63.4	57.9
Other	61.3	49.5
Palpitations	55.9	44.0
Nausea or vomiting	52.2	45.1
Ischemic chest pain	48.9	41.4
Diarrhea	46.8	38.8
Abdominal pain	45.2	34.8
Flushing	43.6	30.4
Rash	43.0	38.1
Fever	33.3	26.4
Syncope	26.3	23.8

[1] Table from the V-HeFT I Medical/Statistical Review

6.1.6.4.3 Incidence of Adverse Events in the V-HeFT II Study

Three percent (13) and 2.7% (11) discontinued BiDil and enalapril as a result of adverse events.

Table 37. Adverse events that led to dose reduction in V-HeFT II

Adverse Event	HYD/ISDN N = 401 %	Enalapril N = 403 %
Headache	40.9	11.2
Fatigue/lassitude	28.9	23.6
Dizziness	26.9	19.4
Other	22.4	17.4
Nausea or vomiting	18.0	13.2
Arthralgia	11.0	6.4
Palpitations	10.2	5.0
Hypotension	7.5	9.7
Abnormal lab tests	7.2	11.2

[1] Table from the V-HeFT I Medical/Statistical Review

Table 38. Incidence of adverse events in V-HeFT II

Adverse Event	HYD/ISDN N = 401 %	Enalapril N = 403 %
Any	98	100
Abnormal lab tests	92	97
Fatigue/lassitude	81	82
Headache	77	60
Arthralgia	69	72
Nasal congestion	68	68
Dizziness	67	67
Other	61	65
Palpitations	57	54
Nausea or vomiting	53	59
Chest pain	44	46
Constipation	42	44

[1] Table from the V-HeFT I Medical/Statistical Review

6.1.6.4.4 Identifying Common and Drug-related Adverse Events

Headache, dizziness, nausea, vomiting, and arthralgia are very likely related to BiDil, and the rational is that they were observed in excess on BiDil, led to withdrawal and/or dose reduction of BiDil, and were consistently associated with BiDil in the A-HeFT and V-HeFT trials.

Hypotension and postural hypotension are also very likely related to the study drug because of its vasodilating action.

6.1.6.4.5 Additional Analyses and Explorations

Table 39. Common adverse events by age categories

Number (%) of patients with at least one AE	<65 years		RR	≥65 years		RR
	BiDil N = 361 n (%)	Placebo N = 376 n (%)		BiDil N = 156 n (%)	Placebo N = 151 n (%)	
Any AE	342 (94.7)	303 (80.6)	*1.2*	133 (85.3)	129 (85.4)	*1.0*
Headache	198 (54.8)	89 (23.7)	*2.3*	58 (37.2)	22 (14.6)	*2.5*
Dizziness	115 (31.9)	46 (12.2)	*2.6*	50 (32.1)	26 (17.2)	*1.8*
Asthenia	49 (13.6)	45 (12.0)	*1.1*	21 (13.5)	14 (9.3)	*1.5*
Nausea	37 (10.2)	19 (5.1)	*2.0*	13 (8.3)	13 (8.6)	*1.0*
Bronchitis	30 (8.3)	26 (6.9)	*1.2*	13 (8.3)	8 (5.3)	*1.6*
Hypotension	29 (8.0)	18 (4.8)	*1.7*	12 (7.7)	5 (3.3)	*2.3*
Peripheral edema	24 (6.6)	25 (6.6)	*1.0*	1 (0.6)	12 (7.9)	*0.1*
Ventricular tachycardia	15 (4.2)	12 (3.2)	*1.3*	6 (3.8)	2 (1.3)	*2.9*
GI disorder	15 (4.2)	11 (2.9)	*2.2*	5 (3.2)	3 (2.0)	*1.6*
Vomiting	15 (4.2)	7 (1.9)	*2.2*	3 (1.9)	3 (2.0)	*1.0*
Palpitations	14 (3.9)	12 (3.2)	*1.2*	6 (3.8)	2 (1.3)	*2.9*
Paresthesia	14 (3.9)	10 (2.7)	*1.4*	4 (2.6)	2 (1.3)	*2.0*
Hyperlipidemia	13 (3.6)	5 (1.3)	*2.8*	2 (1.3)	5 (3.3)	*0.4*
Rhinitis	12 (3.5)	11 (2.9)	*1.2*	7 (4.5)	3 (2.0)	*2.3*
Amblyopia	10 (2.8)	4 (1.1)	*2.5*	6 (3.8)	3 (2.0)	*1.9*
Rash	8 (1.9)	11 (2.9)	*0.7*	5 (3.2)	3 (2.0)	*1.6*
Gastritis	7 (1.9)	4 (1.1)	*1.7*	1 (0.6)	5 (3.3)	*0.2*
Anorexia	6 (1.7)	4 (1.1)	*1.5*	2 (1.3)	5 (3.3)	*0.4*
Anxiety	2 (0.6)	4 (1.1)	*0.6*	5 (3.2)	2 (1.3)	*2.5*
Hematuria	5 (1.4)	1 (0.3)	*4.7*	1 (0.6)	5 (3.3)	*0.2*

Dizziness, nausea, vomiting and gastritis seem to be more prevalent in younger subjects, while ventricular tachycardia, palpitations, and anxiety were more common in older subjects.

Table 40. Common adverse events by gender

	Male gender		RR	Female gender		RR
	BiDil N = 289 n (%)	Placebo N = 228 n (%)		BiDil N = 337 n (%)	Placebo N = 190 n (%)	
Headache	129 (44.6)	55 (16.3)	*2.7*	127 (55.7)	56 (29.5)	*1.9*
Dizziness	83 (28.7)	49 (14.5)	*2.0*	82 (36.0)	23 (12.1)	*3.0*
Hypotension	23 (8.0)	12 (3.6)	*2.2*	18 (7.9)	11 (5.8)	*1.4*
Bronchitis	18 (6.2)	24 (7.1)	*0.9*	25 (11.0)	10 (5.3)	*2.1*
Gout	18 (6.2)	27 (8.0)	*0.8*	9 (3.9)	5 (2.6)	*1.5*
Hypertension	15 (5.2)	22 (6.5)	*0.8*	18 (7.9)	11 (5.8)	*1.4*
Syncope	12 (4.2)	15 (4.5)	*0.9*	11 (4.8)	5 (2.6)	*1.8*
Ventricular tachycardia	11 (3.8)	10 (3.0)	*1.3*	10 (4.4)	4 (2.1)	*2.1*

	Male gender		RR	Female gender		RR
	BiDil N = 289 n (%)	Placebo N = 228 n (%)		BiDil N = 337 n (%)	Placebo N = 190 n (%)	
Amblyopia	11 (3.8)	5 (1.5)	*2.5*	5 (2.2)	2 (1.1)	*2.0*
Paresthesia	10 (3.5)	9 (2.7)	*1.3*	8 (3.5)	3 (1.6)	*2.2*
GI disorder	9 (3.1)	6 (1.8)	*1.7*	11 (4.8)	8 (4.2)	*1.2*
Hyperglycemia	9 (3.1)	13 (3.9)	*0.8*	11 (4.8)	5 (2.6)	*1.8*
Hyperlipemia	9 (3.1)	4 (1.2)	*2.6*	6 (2.6)	6 (3.2)	*0.8*
Insomnia	7 (2.4)	16 (4.8)	*0.5*	16 (7.0)	8 (4.2)	*1.7*
Vomiting	7 (2.4)	5 (1.5)	*1.6*	11 (4.8)	5 (2.6)	*1.8*
Abnormal kidney function	7 (2.4)	6 (1.8)	*1.3*	7 (3.1)	1 (0.5)	*6.2*
Sinusitis	5 (1.7)	1 (0.3)	*5.7*	17 (7.5)	8 (4.2)	*1.8*
Palpitations	5 (1.7)	7 (2.1)	*0.8*	15 (6.6)	7 (3.7)	*1.8*
Rhinitis	5 (1.7)	7 (2.1)	*0.8*	14 (6.1)	7 (3.7)	*1.6*
Nausea vomiting	3 (1.0)	6 (1.8)	*0.6*	8 (3.5)	5 (2.6)	*1.4*
Cellulitis	3 (1.0)	8 (2.4)	*0.4*	8 (3.5)	1 (0.5)	*7*
Hypoglycemia	3 (1.0)	7 (2.1)	*0.48*	7 (3.1)	4 (2.1)	*1.5*
Lung disorder	3 (1.0)	12 (3.6)	*0.28*	7 (3.1)	3 (1.6)	*1.94*
Allergic reaction	2 (0.7)	3 (0.9)	*0.78*	7 (3.1)	3 (1.6)	*1.94*

Hyperlipidemia, hypotension and sinusitis were observed more frequently in males, while bronchitis, syncope, ventricular tachycardia, palpitations, paresthesia, insomnia, abnormal kidney function, nausea/vomiting, rhinitis, cellulites, lung disorders and allergy reactions were more frequent in women.

6.1.7 Laboratory Findings

6.1.7.1 A-HeFT

Laboratory tests were not conducted routinely to either study the effect of the study drug on laboratory parameter or to monitor safety in the study population, and the reason given by the sponsor was that BiDil has a mature and well-known safety profile. Hematology, chemistry and urinalysis were to be conducted only at baseline for reference.

Laboratory test results were reported only when they were determined to be adverse events, and they were determined as such only if they induced clinical signs or symptoms or required a change in therapy, in which case they were recorded on the AE CRF under the signs, symptoms or diagnosis associated with them.

6.1.7.2 V-HeFT

Changes from baseline in selected laboratory parameters in African Americans who participated in the two V-HeFT studies were summarized and a paired t-test was conducted to test the significance of this change.

Table 41. Change from Baseline in Selected Laboratory Parameters in V-HeFT

Parameters and Statistics	Change in Mean from Baseline on HYD - ISDN	p-value

Parameters and Statistics	Change in Mean from Baseline on HYD - ISDN	p-value
Alkaline phosphatase U/L		
N	157	0.052
Range	-71.0 - 167.0	
Mean	6.03	
SD	38.6	
Median	1.0	
BUN units: ml %		
N	158	0.027
Range	-24.0 - 52.0	
Mean	1.63	
SD	9.18	
Median	1.0	
Potassium: mEq/L		
N	157	0.007
Range	-1.6 - 1.5	
Mean	-0.09	
SD	0.44	
Median	-0.1	
Magnesium: mEq/L		
N	108	0.036
Range	-13.0 - 87.0	
Mean	3.24	
SD	15.89	
Median	0.0	
Sodium: mEq/L		
N	158	0.032
Range	-14.0 - 10.0	
Mean	-0.59	
SD	3.45	
Median	0.0	
Hematocrit: %		
N	155	<0.001
Range	-31.0 - 10.0	
Mean	-1.42	
SD	5.19	
Median	-1.0	
Segmented neutrophils		
N	105	0.001
Range	-20.0 - 30.0	
Mean	3.48	
SD	10.53	
Median	4.0	
Urine proteins		
N	108	0.095
Range	-4 - 8.0	
Mean	0.3	
SD	1.83	
Median	0.0	

6.1.8 Vital Signs

6.1.8.1 Overview of Vital Signs Testing in the Development Program

Supine heart rate, SBP and DBP measurements were completed as part of either the complete physical exam that was to be conducted at screening and 6 months, or the brief physical exam that was to be conducted at 3, 6, 9 and 12 months or the final visit.

6.1.8.2 Standard Analyses and Explorations of Vital Signs Data

6.1.8.2.1 Analyses Focused on Measures of Central Tendencies

Table 42. Effect of BiDil on Heart Rate, SBP and DBP, in the A-HeFT Trial

	Heart Rate				Supine SBP				Supine DBP			
	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff
Baseline												
N	516	526	--	--	517	526	--	--	517	526	--	--
Mean	74.2	73.1	--	--	127.2	125.3	--	--	77.6	75.6	--	--
SD	12.3	11.01	--	--	17.5	18.1	--	--	10.3	10.6	--	--
Median	74	72	--	--	128	125	--	--	80	76	--	--
Range	41 to 10	40 to 108	--	--	80 to 196	82 to 185	--	--	39 to 104	47 to 10	--	--
Month 3												
N	435	469	434	468	436	469	436	468	436	468	436	467
Mean	75.5	74.6	1.3	1.3	123.9	126.2	-3.2*	1.1	74.1	75.7	-3.4*	0.3
SD	11.6	11.8	12.19	11.07	19.6	21.8	17.41	17.6	12.7	13.1	12.6	11.5
Median	76	74	2	0	122	124	-2	0	74	76	-2	0
Range	50 to 116	44 to 131	-40 to 40	-36 to 49	80 to 210	74 to 205	-60 to 70	-45 to 70	42 to 130	48 to 130	-35 to 34	-28 to 46
Month 6												
N	388	376	387	375	389	376	389	375	389	376	389	375
Mean	75.8	73.5	1.3	0.0	125.6	125.5	-1.9*	1.2	75.1	76	-2.4*	0.8
SD	12.2	11.8	13.6	11.9	20.8	19.8	18.9	18.3	12.9	13.1	12.3	11.9
Median	76	73	2	0	121	125	-1	0	73	76	-4	0
Range	47 to 114	43 to 112	-41 to 46	-41 to 32	78 to 200	75 to 187	-82 to 602	-50 to 77	42 to 120	40 to 116	-40 to 36	-36 to 56
Month 9												
N	313	306	312	305	313	305	313	304	313	305	313	304
Mean	76.4	74.6	2.3	1.4	123.6	124.7	-4.7*	0.4	74.2	75.6	-3.3*	0.2
SD	12.4	11.5	13.93	13.2	20.5	20.9	20.3	19.1	13.7	13.2	13.2	12.4
Median	76	74	3	0	122	123	-5	1	72	75	-2	0
Range	45 to 10	48 to 106	-40 to 43	-52 to 43	70 to 192	84 to 190	-60 to 69	-50 to 54	42 to 138	40 to 110	-38 to 34	-32 to 46
Month 12												
N	272	257	271	257	276	258	276	258	276	258	276	258
Mean	75.8	74.3	1.5	0.7	124.8	125.6	-3.1*	2	74.4	75.7	-2.8*	0.9
SD	11.8	12.0	13.4	13.0	20.0	19.6	19.3	17.4	12.1	13.5	13.2	12.0
Median	76	74	2	0	124	125	-2	0	74	74	-2	0
Range	50 to 112	42 to 118	-40 to 47	-44 to 64	78 to 200	82 to 182	-54 to 70	-40 to 62	41 to 116	38 to 120	-40 to 38	-34 to 36
Month 15												
N	222	218	221	217	225	218	225	217	225	218	225	217
Mean	76.2	75.7	1.6	1.7	125.7	124.6	-3.1*	0.9	75.1	75.4	-2.9	0.7
SD	11.9	11.7	13.5	11.9	22.2	20.0	21.2	17.7	13.2	13.0	13.3	12.4
Median	76	76	2	0	122	126	-4	2	76	75	-2	0
Range	40 to 120	48 to 110	-47 to 48	-42 to 28	82 to 210	80 to 188	-92 to 68	-60 to 40	43 to 112	48 to 116	-38 to 30	-24 to 48

	Heart Rate				Supine SBP				Supine DBP			
	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff
Month 18												
N	197	176	196	175	197	176	197	175	197	176	197	175
Mean	77.3	73.1	3.0	0.4	125.9	125.6	-3.4*	1.2	75.4	74.8	-3.0*	-0.3
SD	11.2	12.0	12.6	13.7	21.2	19.2	20.4	17.5	13.2	14.0	13.4	12.9
Median	78	72	3	0	124	122	-3	0	74	76	-2	0
Range	48 to 113	49 to 116	-34 to 37	-54 to 52	92 to 200	90 to 180	-62 to 89	-56 to 51	44 to 120	40 to 118	-40 to 30	-40 to 41

*p<0.05, two sample t-test

The difference between BiDil and placebo in the mean change from baseline in heart rate ranged between 0 at 3 months and 2.6 bpm at 18 months.

Differences between BiDil and placebo in mean changes from baseline in supine systolic and diastolic blood pressure were sizable, consistent and statistically significant.

6.1.8.2.2 Marked Outliers and Dropouts for Vital Sign Abnormalities

6.1.8.2.2.1 Bradycardia

There were two cases on BiDil and three on placebo that were determined as serious. No cases led to discontinuation of study drug.

6.1.8.2.2.2 Tachycardia

Tachycardia is a known secondary effect of hydralazine and an excess of ventricular tachycardia was observed on BiDil, Table 31 page 47 and Table 33 page 50.

6.1.8.2.2.3 Hypotension

Hypotension was described as serious in 1.5% (8) and 0.6% (3), and led to discontinuation in 1.4% (7) and 0.6% (3) on BiDil and placebo respectively, Table 31 page 47 and Table 32 page 49. Also, a significant number on BiDil (7.9%) compared to placebo (4.4%) experienced hypotension as a common event, Table 33 page 50.

6.1.8.2.2.4 Diastolic Blood Pressure < 60 mmHg

No difference between the two treatment groups was observed at any follow-up visit in the incidence of a drop in DBP below 60 (incidence ranged between 7% and 13%).

6.1.8.2.2.5 Systolic Blood Pressure < 90 mmHg

Like DBP, no difference between the two treatment groups was observed at any follow-up visit in the incidence of a drop in SBP below 90 (incidence ranged between 1.0% and 3.0%).

6.1.9 The Effect of Concomitant Medication on the Safety Profile

Analyses assessing the effect of concomitant medication on selected adverse events observed in A-HeFT were conducted[8]. The medications considered in these analyses included ACE-I, ARBs, beta-blockers, digitalis glycosides, aldosterone antagonist and other diuretics. The adverse events that were assessed for confounding by concomitant medications included

[8] Analyses completed by the Sponsor

headache, dizziness, pain, chest pain, infection, asthenia, dyspnea, nausea, bronchitis and hypotension.

Adjusting for all concomitant medications in one model and for the medications that seemed to be strong predictors of any adverse event in another model did not explain away the association found between BiDil and headache (OR = 3.7, p-value <0.0001), dizziness (OR = 3.0, p-value <0.0001), nausea (OR = 1.7, p-value = 0.03) and hypotension (OR = 1.9, p-value = 0.02).

6.1.10 Adverse Events Associated with the Components of BiDil

6.1.10.1 Methemoglobinemia associated with ISDN

Methemoglobinemia is an adverse event that is said to occur extremely rarely with ordinary doses of ISDN. No cases were observed in the A-HeFT.

6.1.10.2 SLE-Like Syndrome Associated With Hydralazine

Under PRECAUTIONS, the Hydralazine label says that complete blood counts and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise, or other unexplained signs or symptoms. None of these were completed in A-HeFT. One case of SLE-like syndrome was reported on BiDil but was coded as joint disorder.

6.1.10.3 Hematologic Adverse Events Associated with Hydralazine

Reduction in hemoglobin and red blood cell count, leucopenia, agranulocytosis, purpura, lymphadenopathy and splenomegaly are listed as adverse events associated with hydralazine.

6.1.11 Immunogenicity

The hydralazine component of BiDil is known to trigger hypersensitive reactions and possibly autoimmune-like reactions especially that of SLE. Whether BiDil triggers the same reactions was not evaluated. In the A-HeFT trial, only one patient was reported to have SLE-like syndrome.

Arthralgia and myalgia 2 of the many symptom that are often associated with many autoimmune reactions, were observed in excess on BiDil 1.5% and 1.4% vs. 0.4% and 0.6% respectively.

6.1.12 Human Carcinogenicity

Four cases of neoplasm/carcinoma were observed on BiDil compared to one on placebo.

6.1.13 Special Safety Studies

None completed.

6.1.14 Human Reproduction and Pregnancy Data

There is no information on drug exposure during pregnancy.

6.1.15 Overdose Experience

No cases of overdose were observed.

6.2 Adequacy of Patient Exposure and Safety Assessments

6.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

6.2.1.1 Study Type and Design/Patient Enumeration

6.2.1.1.1 A-HeFT

The primary source of the safety data came from the A-HeFT trial (5.1.5.1 page 20).

6.2.1.1.2 V-HeFT

Data from the V-HeFT studies were used as supportive especially V-HeFT I (5.1.5.2 page 22) that compared BiDil to placebo.

6.2.1.2 Demographics

6.2.1.2.1 A-HeFT

Table 10 page 28.

6.2.1.2.2 V-HeFT

Table 11 page 30.

6.2.1.3 Extent of Exposure (dose/duration)

6.2.1.3.1 Extent of Exposure in the A-Heft Study

Table 43. Extent of Exposure in the A-HeFT study as assessed by duration

	BiDil (N = 517)	Placebo (N = 527)
Duration of exposure, days		
Mean (SD)	298.4 (208.3)	313.8 (197.7)
Median	294	301
Range	1 - 594	4 - 624
Patients on study drug at various time points, n (%)		
3 mon	368 (71.2)	417 (79.1)
6 mon	317 (61.3)	333 (63.2)
9 mon	260 (50.3)	269 (51.0)
12 mon	220 (42.6)	228 (43.3)
15 mon	169 (32.7)	186 (35.3)
	139 (26.9)	146 (27.7)

This table excludes 18-month data, dose of study drug not collected consistently at that visit.

Table 44. Extent of Exposure in the A-HeFT study as assessed by total number of tablets taken per day

Total tablets/day[1]	BiDil (N = 517)	Placebo (N = 527)	Total tablets/day[1]	BiDil (N = 517)	Placebo (N = 527)
3 Month			**9 Month**		
N[2]	368	417	n[2]	260	269
Mean (SD)	4.4 (2.1)	5.0 (1.9)	Mean (SD)	4.8 (1.9)	5.2 (1.7)

Total tablets/day[1]	BiDil (N = 517)	Placebo (N = 527)	Total tablets/day[1]	BiDil (N = 517)	Placebo (N = 527)
Median	6	6	Median	6	6
Range	0 - 6	0 - 6	Range	0 - 6	0 - 6
6 Month			**12 Month**		
N[2]	317	333	n[2]	220	228
Mean (SD)	4.5 (2.0)	5.1 (1.8)	Mean (SD)	4.8 (1.9)	5.3 (1.6)
Median	6	6	Median	6	6
Range	0 - 6	0 - 6	Range	0-6	0-6
15 Month					
n[2]	169	186	Median	6	6
Mean (SD)	4.9 (1.7)	5.3 (1.7)	Range	0 - 6	0 - 6

This table excludes 18-month data; dose of study drug not collected consistently at that visit;
[1] Total number of tablets recorded on Study Drug Administration CRF if frequency was not t.i.d. or calculated by multiplying "# of tablets" by 3 (if frequency of t.i.d. was recorded);
[2] Number of patients with dosing information at indicated time point;

As can be seen from the table above, on average, patients took 4 ½ tablets per day at 6 months. Translated to milligrams, patients took on average 169/90 mg of BiDil per day. The average intake increased by close to ½ a tablet from Month 3 visit to 184/98 mg at Month 15. Exposure, whether measured in days or in number of tablets per day, seems to be slightly lower for BiDil compared to placebo.

6.2.1.3.2 Extent of Exposure in the V-HeFT African-American Population

Table 45. Summary of Drug Exposure to HYD – ISDN for African-American Patients in the V-HeFT Trials

Statistics	Values
Time on Study	
N	158
Range	3 – 2009
Mean	994.6
SD	550 – 51
Median	1032
Documented Days on BiDil	
N	158
Range	0 – 2045
Mean	812.3
SD	551.5
Median	727

The sponsor provided extent of exposure only for patients on active treatment.

6.2.1.4 Literature

Information sought by the reviewer included publications about the incidence of SLE on hydralazine and that of methemoglobinemia on organic nitrate therapy..

6.2.2 Adequacy of Overall Clinical Experience

The pivotal trial study design, number of subjects exposed, and duration of exposure to the study drug were adequate.

The A-HeFT assessed the target dose combination of 225/120, and the V-HeFT studies assessed 300/160 mg.

The pivotal study was limited to one ethnic group, and the findings of the BiDil program do not provide evidence to support the use of BiDil in non-African-American subjects.

6.2.3 Adequacy of Special Animal and/or In Vitro Testing

BiDil is a combination of two components already marketed for cardiovascular diseases.

One potential safety issue that was raised in the July-2d-1997 non-approvable letter concerned the potential of carcinogenicity as a result of a possible interaction between the drug substances and the formation of N-nitrosamines. The Sponsor responded to this in an amendment to the NDA in November 2001. For evaluation of the sponsor's response to this concern, refer to the Chemistry review.

6.2.4 Adequacy of Routine Clinical Testing

6.2.4.1 See 6.2.6, page 62

6.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

6.2.5.1 See Drs. Hinderling and Velazquez Reviews

6.2.6 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Hydralazine and isosorbide dinitrate are two components that have been marketed in the US. Also the BiDil combination has been reviewed by the Division in an NDA submission in July 1996.

One of the recommendations of the hydralazine label, the completion of blood counts and antinuclear antibody titers before and periodically during prolonged therapy, was not completed.

6.2.7 Assessment of Quality and Completeness of Data

Except for data assessing the effect of the hydralazine component on the immune system, the data available for conducting safety review was relatively complete. These data included adverse events by seriousness and/or whether they led to study drug discontinuation, and by categories of age, gender and treatment. It also included narratives of SAEs and life threatening and fatal events.

V-HeFT safety information summarized in this review is a duplicate of the safety summary in the clinical and statistical reviews completed by the Division in 1997. The latter reviews did not summarize less frequent adverse events because they were merged by the sponsor into the category of "other".

6.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Systemic lupus erythematosus:

One case of SLE-like syndrome was observed during the trial. Given the known association between hydralazine, a component of BiDil, and this adverse event, it is likely that this case is associated with BiDil. The patient while still taking BiDil was treated and the symptoms resolved, but there is no data on what happened after the termination of the treatment of SLE.

Arthralgia was observed at an incidence that is almost 4 times as high as that observed on placebo, Table 33 page 50.

Malaise was 6 times as high on BiDil as on placebo, Table 33, page 50.

Myalgia was more than 2 times as high on BiDil as placebo, Table 33 page 50.

Antinuclear antibody titers determination tests should have been conducted in these patient as per the hydralazine label.

Angioedema

A case of angioedema did not resolve completely after discontinuation of benazepril and treatment but did after discontinuation of BiDil. However, the narrative said that study drug was to be restarted 3 days later, but there was no information on what happened after restarting the study drug.

Another case of angioedema that developed 4 days post study drug initiation and resolved after treatment and discontinuation of study drug without discontinuing the patient's ACE inhibitors therapy.

A third case of angioedema that developed 6 days after study drug initiation and resolved with treatment and discontinuation of study drug.

The incidence of angioedema was 6 times higher on BiDil than on placebo, Table 33, page 50.

Clinically significant hypotension

Hypotension that led to a visit to the ER and/or hospitalization was observed in 7 subjects on BiDil. The causal association is very likely given that both component of BiDil could cause and/or predispose to hypotension.

Twice and ½ as many BiDil as placebo subjects developed hypotension as a serious adverse event;

Ventricular tachycardia

An excess was observed on BiDil, Table 33 page 50;

Almost twice as many BiDil as placebo subjects developed serious ventricular tachycardia, Table 31, page 47;

This was more common in older (≥ 65 year) and female subjects;

The association is stronger in the elderly subjects;

Tachycardia

Observed in almost twice as many BiDil as placebo subjects, Table 33 page 50;

It is listed in the hydralazine label as a common adverse event;

Supraventricular tachycardia

Observed in 4 BiDil vs. no placebo subjects;

Headache

The incidence on BiDil was more than twice a high as that on placebo, Table 33, page 50;

Headache is known to be causally related to the ISDN component of BiDil;

Dizziness

The incidence on BiDil was more than twice as high as that on placebo; Table 33, page 50;

This is known to be associated with hydralazine;

Somnolence

It was observed in almost 4 as many BiDil as placebo subjects, Table 33 page 50;

Asthenia

This led to discontinuation in 11 and ½ as many BiDil as placebo patients, Table 32 page 49;

Nausea and Vomiting

Incidence rates on BiDil were each more than 1 ½ as high as those on placebo, Table 33 page 50;

These are known to be associated with hydralazine;

Amblyopia

The incidence on BiDil was more than twice as high as that on placebo, Table 33 page 50;

Abnormal vision was also observed in 4 BiDil vs. 2 placebo subjects;

Hyperlipidemia and hypercholesterolemia

Hyperlipidemia was observed in 50% more on BiDil compared to placebo, Table 33 page 50;

Hypercholesterolemia was observed in 3 ½ as many subjects on BiDil as on placebo, Table 33 page 50;

Abnormal kidney function

This was observed in twice as many BiDil as placebo subjects, Table 33 page 50;

Uremia was observed in 2 additional BiDil subjects;

It could be secondary to hypo-perfusion of the kidney as a result of hypotension;

Cerebral ischemia + infarct

This was observed in 3 as many BiDil as placebo patients;

Could hypoperfusion have triggered or complicated this event?

Coronary artery disease

This was observed in almost twice as many BiDil as placebo subjects, Table 33,

page 50;

Cardiovascular disease

Coded as such in 5 BiDil vs. no placebo subjects;

Chest pain

This led to discontinuation in almost 4 as many BiDil as placebo subjects, Table 32 page 49;

Known to be associated with hydralazine, per the label;

Neoplasm

Neoplasm observed in twice as many BiDil as placebo subjects, Table 33 page 50;

Sweat increase, alopecia, cholecystitis

These were also observed at a higher incidence on BiDil than on placebo;

6.4 General Methodology

6.4.1 Pooled Data vs. Individual Study Data

Only one study was prospectively conducted and submitted for review of the proposed indication. Supportive data were submitted in the 1996 NDA, and post hoc safety analyses by race were conducted and submitted with the current NDA. Data were not pooled because firstly the V-HeFT studies were not designed to assess the effect of BiDil solely in African Americans; secondly the regimen and the schedules of exposure and adverse event assessments used were different; thirdly, the African-American sub-population of the V-HeFT I and the population of A-HeFT seem to be different with regard to background, placebo-associated, rates of common adverse events; and lastly, the medical management of both populations must be different for the medical management of HF has changed since the time V-HeFT I was conducted.

6.4.2 Explorations for Predictive Factors

6.4.2.1 Explorations of Time Dependency for Adverse Findings

Headache and dizziness started within a week, and nausea and hypotension started within a month of BiDil initiation.

6.4.2.2 Explorations for Drug-Demographic Interactions

This has already been completed in section 6.1.6.4.5, page 54 with regard to the common adverse events.

Additional information can be deduced from analyses completed as part of the exploration of the effect of BiDil on the composite score of all cause mortality + first hospitalization for HF + change in QOL by gender and age, Figure 5 page 40.

BiDil seems to have the same effect on all-cause mortality and hospitalization for HF in both genders and in younger and older subjects.

6.4.2.3 Explorations for Drug-Disease Interactions

This was not conducted as a part of adverse event analyses, but information on the effect of this interaction on mortality and hospitalization can be deduced from analyses completed as part of the exploration of the effect of BiDil on the composite score of all cause mortality + first hospitalization for HF + change in QOL in subpopulations with DM, chronic renal insufficiency, ischemic etiology of HF, and history of hypertension, Figure 5 page 40.

As can be see from the figure, the presence of other co-morbidities did not change the effect of BiDil in these subgroups one way or another.

6.4.2.4 Explorations for Drug-Drug Interactions

Confounding of most common AE by concomitant drugs was explored, see 6.1.9 page 58.

Additional information can be deduced from analyses completed as part of the exploration of the effect of BiDil on the composite score of all cause mortality + first hospitalization for HF + change in QOL by drug categories of ACE-I, ARBs, beta-blockers, CCBs, aldosterone antagonists, non-aldosterone antagonist diuretics and digoxin, Figure 5 page 40.

As can be seen from the figure, BiDil did not interact in a negative way with other drugs.

Interaction with other medications with regard to serious less common AEs was not explored. Therefore, one cannot exclude the potential for a deleterious interaction with any of the concomitant drugs that a HF patient is usually exposed to.

6.4.3 Causality Determination

6.4.3.1 Adverse Events Likely Causally Related to BiDil

Events that are likely causally attributed to BiDil with a certain level of assurance in this study population are headache, dizziness, nausea and vomiting, hypotension, chest pain, asthenia, tachycardia and palpitations, and paresthesia. These events were observed in excess on BiDil, the components of BiDil are labeled for some of these adverse events, and BiDil or any of its components have the mechanistic ability to generate these adverse events.

6.4.3.2 Adverse Events Probably Causally Related to BiDil

Events that are probably causally related to BiDil include arthralgia, myalgia and malaise which were observed in excess on BiDil and could have been symptoms of the SLE-like syndrome attributed to hydralazine; and angioedema because of hydralazine's tendency to affect the immune system.

Somnolence which was observed in excess on BiDil;

6.4.3.3 Adverse Events Possibly Causally Related to BiDil

Events that are possibly causally related to BiDil include abnormal kidney function because of its excess on BiDil and the possibility of hypoperfusion as a triggering factor; likewise cerebral ischemia because of its excess on BiDil and the possibility of hypoperfusion as a triggering factor; and ventricular tachycardia;

7 ADDITIONAL CLINICAL ISSUES

7.1 Dosing Regimen and Administration

The A-HeFT trial studied a lower dose and a different regimen than what was previously (V-HeFT I and II) targeted for heart failure, 75/40 mg t.i.d. instead of q.i.d. The lower dose or A-HeFT data were robust and significant in showing the efficacy of BiDil in the AA study population. Data from the higher dose/regimen showed no efficacy on HF in the population studied, but post-hoc analyses showed a trend toward efficacy in the African-American subpopulation, especially in V-HeFT I.

Comparing the most common adverse events (headache and dizziness) in both dosing regimens, both BiDil and placebo subjects in V-HeFT I experienced more of these events than did subjects in A-HeFT, and despite the reduced incidence in A-HeFT, the association between BiDil and these adverse events was stronger than in V-HeFT.

7.2 Interaction with Other Anti-hypertensive Therapies

If approved as a treatment for heart failure, BiDil may be added to other HF treatment regimens which may include other significant antihypertensive medications. Given that BiDil lowers blood pressure and causes hypotension in some patients, it is likely that it could aggravate the risk of hypotension in HF subjects who will not be followed as closely as the A-HeFT subjects were. Therefore, the reviewer recommends initiating BiDil and tapering it slower than it was in A-

HeFT, especially if subjects are receiving the beta-blocking agents that were found to interact with hydralazine (e.g., metoprolol, propanolol).

7.3 Special Populations

The effect of BiDil on heart failure was shown to be positive in African American patients only. BiDil did not seem to have an effect in non-African-American HF patients.

Subgroup analyses by age and gender showed that despite the small number of events in these sub-populations, a trend of effect on the composite endpoint was maintained.

7.4 Pediatrics

A deferral for a pediatric program was granted.

7.5 Advisory Committee Meeting

An advisory committee meeting to discuss the findings of BiDil is scheduled for June 16, 2005.

7.6 Literature Review

The information from literature search provided by the sponsor included the following:

-Publications about the pathophysiology of heart failure;

-Pathophysiological differences that could account for potential race differences in disease outcomes especially those of heart failure;

-Potential mechanism and role played by hydralazine in preventing or deterring tolerance to isosorbide dinitrates;

8 OVERALL ASSESSMENT

8.1 Conclusions

The A-HeFT study has shown that BiDil reduced mortality and the risk of HF hospitalization in African-American heart failure patients. Even though the reduction of mortality was not the primary endpoint, the study was terminated as a result of an effect on mortality that was observed before the study was due to end.

The safety profile of BiDil in A-HeFT was not very different from that of placebo. Given that BiDil had a beneficial effect on all-cause mortality, any adverse event no matter how severe it is, it would be relatively tolerable in this population.

The proposed indication per the label is the treatment of CHF in black patients who are either intolerant or have a contraindication to ACE inhibitors therapy, but the patients studied in the pivotal trial were not enrolled based on their intolerance or the contra-indication to ACE inhibitors . Therefore the reviewer concludes that BiDil should be indicated in the same population in whom it was studied in the A-HeFT study.

8.2 Recommendation on Regulatory Action

Based on the clinical results of A-HeFT, BiDil could be safe and effective in African-American subjects suffering from heart failure.

8.3 Recommendation on the Label

8.3.1 Trial Design

The label should state that A-HeFT was not designed to show that the combination was superior to either of its components. This way it won't indirectly be concluded that either hydralazine or isosorbide dinitrate is inferior to the combination of both.

8.3.2 Intended Population for Indication

If approved, BiDil should be indicated for the treatment of chronic heart failure in all blacks, not only in those who are intolerant or have a contraindication to ACE inhibitors as the proposed label says.

8.3.3 Mechanism of Action

The label should include language regarding the difference in blood pressure control between the treatment groups throughout the trial, and the possibility of this difference accounting, at least partly, for the observed effect.

8.3.4 Medication Regimen

The label should recommend a titration of BiDil over at least a week to prevent discontinuations for headache and dizziness.

9 APPENDICES

9.1 A-HeFT Protocol Amendments (Sponsor's Tables)

Table 46. Summary of protocol amendments related to changes in entry and randomization criteria

Original entry criterion	Modification	Reason for change	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Inclusion criterion #3				
Have stable, chronic HF, NYHA class III-IV, diagnosed at least 3 months prior to Screening.	3. Have stable, chronic HF diagnosed at least 3 months prior to Screening 4. Have NYHA class III-IV at the time of Screening.	Clarified that NYHA class III-IV requirement applies to assessment at Screening visit. Patient was not required to have NYHA class III-IV HF for at least 3 months prior to Screening.	05 (Dec. 12, 2001)	112 (10.7)
Inclusion criterion #4 (renumbered to #5 with Protocol amendment #5, Dec. 12, 2001)				
…Patients receiving beta blockers must have been taking these for at least 6 months…	…Patients receiving beta blockers must have been taking these for at least 3 months.	Decreased requirement for time on beta blocker prior to screening.	02 (Jun. 15, 2001)	2 (0.2)
Inclusion criterion #5 (renumbered to #6 with Protocol amendment #5, Dec. 12, 2001)				
Have a resting LVEF <35% (by any method) and a resting LVIDD >2.9 cm/m^2 BSA or >6.5 cm (by echocardiogram) obtained anytime within the prior 6 months using the most recent values available.	Have a resting LVEF ≤35% (by any method) and a resting LVIDD >2.9 cm/m^2 BSA or >6.5 cm (by echocardiogram) obtained anytime within the prior 6 months using the most recent values available.	Changed LVEF entry criteria from <35% to ≤35%.	03 (Aug. 1, 2001)	10 (1.0)
	Have either a resting LVEF ≤35% (by any method) or a resting LVIDD >2.9 cm/m^2 BSA (or >6.5 cm) with LVEF < 45% (by echocardiogram) obtained anytime within the prior 6 months using the most recent values available.	Changed criteria for LV dysfunction to permit abnormal LVEF or abnormal LVIDD (as long as LVEF <45%).	04 (Oct. 22, 2001)	55 (5.2)

Original entry criterion	Modification	Reason for change	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Inclusion criterion #7				
Have had at least one hospitalization for heart failure during the preceding year, as judged by the investigator."	Criterion deleted.	Eliminated entry criterion in order to enhance recruitment, based on decreasing number of hospitalizations due to change in standard of care to more frequent outpatient management.	08 (Mar. 25, 2003)	544 (51.8)
Criteria for stability				
Procedures to be done at the Baseline Visit: "Confirm that the patient has been stable since the screening visit…"	"Confirm that the patient has been stable for at least 2 weeks since the screening visit…"	Clarified time period for stability of symptoms and HF therapy	02 (Jun. 15, 2001)	2 (0.2)
At Baseline visit, patients are eligible for randomization if: "Body weight has not changed by more than 2%."	At Baseline visit, patients are eligible for randomization if: "Body weight has not changed by more than 2.5% relative to Screening Visit body weight."	Broadened stability criteria to clarify acceptable weight change limits.	04 (Oct. 22, 2001)	55 (5.2)
Exclusion criterion #4:				
Have coronary artery disease likely to require coronary artery bypass grafting or PTCA during the study period.	Have coronary artery disease likely to require coronary artery bypass grafting or percutaneous transluminal coronary angioplasty during the ensuing year.	Specified a time period for the anticipated clinical event constituting the exclusion.	01 (May 3, 2001)	0 (0)
Exclusion criterion #5:				
Have symptoms of unstable angina or angina precipitated by exercise within 3 months.	Have symptoms of unstable angina within 3 months prior to screening.	Clarified definition of unstable angina (removed "angina precipitated by exercise") and timeframe for exclusion.	01 (May 3, 2001)	0 (0)
Exclusion criterion #6:				
Have had cardiac arrest, ventricular tachycardia or another severe ventricular arrhythmia considered life threatening within 3 months unless treated with an implantable cardiac defibrillator.	Have had cardiac arrest or a sustained ventricular tachycardia considered life threatening and requiring intervention within 3 months, unless treated with an implantable cardiac defibrillator	Clarified definition of arrhythmia considered exclusion.	01 (May 3, 2001)	0 (0)

Original entry criterion	Modification	Reason for change	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Exclusion #9				
Have rapidly deteriorating or uncompensated HF such that consideration for cardiac transplantation would be likely over the ensuing year.	Have rapidly deteriorating or uncompensated HF such that cardiac transplantation would be likely over the ensuing 1 year.	Clarified timeframe for the anticipated clinical event constituting the exclusion.	01 (May 3, 2001)	0 (0)
Exclusion #14				
Have received any other investigational drugs within 3 months.	Have received another investigational drug or device within 3 months prior to screening.	Added exclusion of investigational device, clarified timeframe.	01 (May 3, 2001)	0 (0)
Exclusion criterion #15				
Currently require sildenafil (Viagra®).	Currently require… phosphodiesterase-5 inhibitors like sildenafil (Viagra®), vardenafil (Levitra®), or tadalafil (Cialis®…"	Specify that all available phosphodiesterase-5 inhibitors are excluded.	09 (Aug. 26, 2003)	700 (66.7)

Table 47. Summary of protocol amendments including additions or changes to study assessments

Assessment added or changed	Comment	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
LV wall thickness assessment added to echocardiographic measurements of LVEF and LVIDD.	Secondary efficacy assessment added.	01 (May 3, 2001)	0 (0)
Echocardiographic measurements to be done at baseline and at six months rather than at every three month visit	Echocardiographic measurements limited to baseline and at 6 months.	01 (May 3, 2001)	0 (0)
Urine pregnancy test added to serum pregnancy test as test permitted to determine pregnancy at baseline	Additional option added for baseline assessment of pregnancy.	01 (May 3, 2001)	0 (0)
Change in echocardiographic assessments from blinded reading by a central laboratory to blinded reading by an external expert. Core Laboratory to inspect echocardiograms for acceptability/readability.	Changed responsibility for secondary efficacy variable assessment.	04 (Oct. 22, 2001)	55 (5.2)

Table 48. Summary of protocol amendments including changes in study procedures

Procedure added or changed	Comment	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Scheduling of baseline visit: Timing of visit relative to screening visit changed from two weeks +two days to two weeks +seven days	Allowed additional flexibility in baseline visit scheduling.	01 (May 3, 2001)	0 (0)
Addition of second baseline visit: Patients who were considered not eligible for randomization at baseline could have a second baseline visit scheduled, to occur no more than two weeks after the first baseline visit. Patients who failed to qualify for randomization at the second baseline visit were not to have another baseline visit but could, at the investigator's discretion, begin the screening process over again at a future visit.	Allowed patients who failed to qualify for randomization an additional opportunity to qualify.	01 (May 3, 2001)	0 (0)

Procedure added or changed	Comment	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Scheduling of baseline visits: Timing of baseline visit relative to screening visit changed from two weeks +seven days to maximum of 28 days; patients were to be stable in the 14 days prior to the baseline visit.	Allowed additional flexibility in baseline visit scheduling but maintained randomization criteria for stability	02 (Jun. 15, 2001)	2 (0.2)
Timing of baseline visits: Timing of second baseline visit (if patient failed to qualify on first baseline visit) specified as no more than 28 days after screening visit.	Limited maximum duration between screening and randomization to 28 days for patients who required a second baseline visit.	02 (Jun. 15, 2001)	2 (0.2)

9.2 Discrepancies in Adjudication of Cause of Death

Table 49. Investigator-assigned causes of death for patients assessed by ICAC as having deaths due to non-cardiovascular causes

Treatment Patient number	Investigator cause of death
BiDil	
012-014	Cardiopulmonary arrest, hypotension, metabolic acidosis
046-003	Hepatic failure
107-033	Death due to stomach cancer
Placebo	
038-006	Exacerbation of CHF
059-010	Hemoptysis
089-008	Respiratory failure
090-030	Cardiopulmonary arrest
240-001	Cardiac arrest

9.3 Additional Information on V-HeFT I and V-HeFT II

For more information on these two studies, refer to the Division's Reviews.

NDA: 20-727

Reviews: Medical and statistical

Reviewers: James Hung, Ph.D., Shaw Chen, MD., Charles J. Ganley, MD.

Date of completion: 03/04/1997

9.4 Study Committees

9.4.1 ICAC (the Independent Central Adjudication Committee)

An independent review committee referred to as was to adjudicate death, all hospitalizations, unscheduled ER and Office visits, and new heart transplant listing. The committee was composed of 6 cardiologists who are experienced in the diagnosis and treatment of cardiovascular diseases.

The committee was divided into teams of 2 and each team reviewed a number of cases, presented the cases in a meeting where they were discussed and voted on by all committee members.

Death was to be classified as due to HF, other cardiac cause or non-cardiac cause, and as sudden and non-sudden cardiac death.

Hospitalization

9.4.2 DSMB (Data and Safety Monitoring Board)

The Data and Safety Monitoring Board was comprised of for members and these were:

David DeMets, Ph.D. Department of Biostatistics and Medical information, University of Wisconsin, Madison, WI;

Richard Grimm, M.D., Hennepin County Medical Center, Minneapolis, MN;

Pamela Ouyang, M.D., Department of Cardiology, John Hopkins University Medical Center, Baltimore, MD;

Jackson Wright, M.D. Department of Medicine-Hypertension, Case Western Reserve University School of Medicine, Cleveland, OH;

Dr. Ralph D' Agostino was the statistician responsible for the overall data analyses and for preparing the reports that DSMB was to review.

The committee was to be independent and to review data mainly to adjust for the sample size since an accurate estimate of the needed sample size was not possible as a result of the lack of data on the composite primary endpoint.

Interim analyses were to occur periodically and Dr. Ralph was to prepare the data and code it to maintain the blind of the committee as long as possible.

Data to be reviewed include:

Total enrollment at time of review;

Baseline data by treatment groups A and B;

Total number and timing of all SAEs;

Total number and timing of all clinical endpoints;

Listing of all SAEs;

Table summary of all SAEs grouped into treatments of A and B;

Table summary of all investigator-reported clinical endpoints;

Table summary of all investigator-reported clinical endpoints grouped into treatments A and B;

Table summary of all adjudicated clinical endpoint events by treatment groups A and B;

Tables of clinical endpoints and SAEs by protocol specification subgroups;

Other statistical analyses as requested;

9.5 Narratives

Patient 190-003 is a 40 year-old female with HF secondary to "dilated post-partum cardiomyopathy" and hyperlipidemia, cerebrovascular disease, previous myocardial infarction, past history of angina, depression, asthmatic bronchitis, and obesity. Approximately one year after the initiation of treatment the patient developed "lupus-like symptoms", which were assessed as being of moderate severity. She was treated with hydroxychloroquine (Plaquenil®) for these symptoms, which resolved after approximately seven weeks. There was no change in study drug administration as a result of this adverse event.

Patient 041-002, a 53-year-old female, who 34 days after randomization to BiDil, presented to the ER with swelling of the upper lip. On exam she had an urticarial rash. She was given diphenhydramine and prednisone, had her benazepril discontinued and her swelling improved post discharge. Four days later, she retuned to the ER with increased lip swelling that was worse one hour after ingesting the study drug. She was treated with prednisone diphenhydramine and ranitidine, and the study medication was stopped. Another four days later she was seen in follow-up, her swelling had improved, and her study drug was to be restarted in 3 days.

Patient 044-005

This 46-year-old male developed angioedema and was seen in the ER four days after being on study drug. He was treated with diphenhydramine, dexamethasone, ranitidine and methylprednisone. He was discharged, study drug was discontinued, but his other medications including fosinopril were not modified. The patient recovered completely.

Patient 067-006

This 64-year-old female developed clinically significant hypotension, 77/50, 30 minutes after taking her first pill of the study drug in the study site clinic. The patient was given fluids and monitored for 1 ½ hours before she was discharged into the care of her daughter. The study drug was discontinued and the patient refused to restart it.

Subject 108-027

This 69-year-old male presented to the ER 3 months and 19 days after been randomized to study drug with weakness and diaphoresis and was found to by hypotensive 70/32. Apparently the patient experienced similar episode for which he was hospitalized after being on the drug for 2 months and was instructed to discontinue the study medication, but the patient said that he had continued taking it.

Patient 121-007

This 48-year-old female presented to the ER 4 days after starting the study drug with a complaint of weakness for the last 24 hours. Her BP was found to be 81/43 mmHg. She was treated with IV 1,000 cc of normal saline, her BP rose to 111/63 mmHg, she felt better and was discharged. The patient recovered and no change in medication was made.

Patient 144-013

This 62-year-old female presented to the ER 19 days after starting the study drug. She was found to have hypotension 63/35 mmHg. It was determined that there was a recent doubling of her carvedilol dose and of the study drug as well. The patient was hospitalized, she was treated with IV hydration, and all antihypertensive medications and the study drug were withheld.

Home medication regimen was slowly incorporated back to prehospital dosages, except for the study medication that was held and carvedilol given at ½ the prior dose. Four days after ER visit, her BP was 134/88 mmHg and she was discharged.

Patient 199-008

This 52-year-old female experienced a syncopal episode 1 ½ hours after her first dose, and was reported unconscious for approximately 1 minute and when conscious complained of dizziness. Patient was transported to the ER where her BP was found to be 70/40 mmHg, hydrated and labs done that revealed renal insufficiency. The study drug was discontinued, toresemide was reduced to 60 mg b.i.d. and she was discharged one day later.

Patient 261-007

This 76-year-old female experienced lightheadedness, nausea, diaphoresis and generalized weakness two days after she had her study drug titrated up to 2 tablets b.i.d. She skipped her midday dose and took her second dose at night. Her symptoms persisted overnight and the following day she called 911 and was transported to the ER. She was diagnosed with a pre-syncopal episode that was felt "almost certainly" related to study medication. The study drug was discontinued and the patient recovered.

Patient 006-001

This 75-year-old male Information with a history of congestive heart failure, adenocarcinoma of the prostate, coronary artery disease, hypertension, hyperlipidemia, aortic insufficiency, mitral regurgitation s/p aortic valve prosthesis, s/p CABG, s/p bi-ventricular pacemaker, s/p AICD and chronic obstructive pulmonary disease. Two months and 15 days later after study drug initiation, he was seen at the emergency room due to firing of the AICD. The patient lost consciousness after the first time the device fired. The AICD was interrogated and found to have ventricular tachycardia at 280 msecs with AICD shocks. The study drug was interrupted.

Patient 009-004

This 47-year-old male with a history of congestive heart failure, idiopathic dilated cardiomyopathy, hyperlipidemia, and GERD. On 27-Dec- 2001 the subject was randomized to receive either BiDil or placebo in addition to current therapy.

Nine months after being on the study drug, the patient complained of increasing shortness of breath with exertion and at rest and difficulty sleeping when he presented for a month protocol follow-up visit. The patient was admitted directly from the office for further management. His heart showed an apical systolic murmur and the EKG-poor R wave progression. The patient was treated with dobutamine and intravenous diuretics. 4 days later, the patient experienced an episode of ventricular tachycardia, and he had an AICD placed. There were no complications. The patient was discharged one day later. The subject completely recovered and no action was taken regarding study medication.

Patient 010-012

This 56 year-old male, with a history of congestive heart failure, idiopathic dilated cardiomyopathy, hypertension, COPD, headaches, insomnia, s/p bladder surgery, PVCs, non-sustained ventricular tachycardia, mitral regurgitation, tricuspid regurgitation and seasonal allergies who after one month and 10 days of being on BiDil he was seen in consultation and a holter monitor demonstrated significant ventricular ectopy and short runs of non-sustained ventricular tachycardia. All of these episodes were asymptomatic. The patient was not

recommended to have an EP study and not to have an AICD placed at that time. The patient was suggested to start on a beta-blocker and return for follow-up in one month. Twenty six days later, the patient returned for follow-up and a repeat Holter monitor confirmed that there was no significant change to his ventricular ectopy. The recommendation was to increase the dose of the beta-blocker and repeat the Holter study. Another 26 days later, the patient was seen by his primary physician who noted significant PVCs, bigeminy, trigeminy, and runs of non-sustained ventricular tachycardia on EKG. Because of the PVCs the patient was admitted to the hospital for further evaluation. The patient was originally treated with lidocaine via drip and enoxaparin. The patient was seen in consultation by a cardiologist who suggested increasing the beta-blocker. The enoxaparin and lidocaine were subsequently discontinued and the patient was treated with clopidogrel. His oral digoxin dose was also increased. The patient had a chest CT that demonstrated a right middle lobe infiltrate and also a probable thoracic aneurysm. After discussion, the patient was transferred to another hospital for further evaluation and management, and he was subsequently discharged 4 days later.

Patient 012-017

This 48-year-old male, with a history of CHF, hypertension, atrial fibrillation, hyperlipidemia, COPD, mitral valve disease, s/p CABG, s/p MI, dizziness, nausea, near syncope, headaches, sinusitis, myopia, constipation, lower extremity numbness, s/p URI, obesity, s/p pericardial effusion and tricuspid regurgitation, went to ER 6 days after initiation of BiDil with a complaint of severe dyspnea, fatigue, chest and abdominal pain that lasted for 24 hours. The patient was not able to achieve relief with sublingual nitroglycerin and called the EMT, and he was admitted for evaluation. During the hospital stay, the patient was observed to have numerous episodes of ectopic beats and occasional runs of ventricular ectopy. None of these caused any significant clinical abnormalities. No specific treatment was prescribed for the ectopy. The patient slowly improved and was discharged 7 days later. The subject completely recovered and no action was taken regarding study medication.

Patient 012-018

This 62-year-old female with a history of CHF, cardiomyopathy, hypertension, atrial fibrillation, s/p TIA, mitral and aortic valve disease, s/p mastectomy, elevated liver function tests, glucose intolerance, hypokalemia, pulmonary hypertension, tricuspid regurgitation, anemia, arthritis, indigestion, depression, anxiety, headaches, s/p hysterectomy, hyperopia and constipation, presented to the Emergency Room with a complaint of nausea and being “sick” about 3 months after being on BiDil. The patient had run out of medication 2-3 days prior to presentation. In the ER, the patient was given medicine for BP and sedation and felt better. On examination she was hypertensive. EKG showed sinus rhythm with LVH. Chest X-Ray showed cardiomegaly. Lab data revealed BNP >5000, CK-708, CKMB 20.4, Troponin 0.03 and WBC 9,000. The patient was admitted for further evaluation. The patient was treated with IV diuretics. The patient had an episode of non-sustained ventricular tachycardia. She was started on amiodarone. The patient had a good response to diuretics and lost 12 lbs. BP also improved but was still sub-optimal. The patient slowly improved and was discharged 4 days later. The subject completely recovered and no action was taken regarding study medication.

Patient 032-007

This 72-year-old female with a history congestive heart failure, hypertension, hyperlipidemia, peripheral vascular disease, mitral valvular disease, s/p CABG and s/p MI, presented to the ER

5 months after initiating BiDil with complaints of chest pain radiating to the right arm associated with shortness of breath and nausea. The patient was treated with a nitroglycerin drip and also given enoxaparin and morphine. EKG showed St-T wave depression in the infero-lateral leads. Two days later, the patient underwent coronary angiography that demonstrated an 80% discrete ostial LAD lesion, a 100% proximal LAD lesion, a 100% ostial left circumflex lesion and a 100% proximal RCA lesion. The SVG to RCA had a 100% proximal lesion. There were no lesions in the SVG to LAD or SVG to Circumflex. It was elected to treat the patient medically. Three days later, the patient had an 18 beat run of non-sustained ventricular tachycardia with a heart rate of 122 beats per minute. There was no evidence to indicate additional treatment was required or that the ventricular tachycardia recurred. The patient was discharged to home the same day, and no change in study drug administration was made.

Patient 037-002

This 52-year-old male with a history of congestive heart failure, idiopathic cardiomyopathy, hypertension, atrial fibrillation, s/p CVA, chronic renal insufficiency, gout, hypercholesterolemia and polyarticular arthritis, presented to the hospital after being on BiDil for 4 months and 25 days with a three-day history of dyspnea, PND, orthopnea and weight gain associated with a non-productive cough. The patient also had intermittent chest pain radiating to the back for three days without aggravating factors. Two weeks before admission, patient's digoxin was held due to high levels. The patient also noted decreased urine output with lightheadedness. In the ER, patient was hypotensive and tachycardic. Chest X-Ray showed cardiomegaly with pulmonary vascular congestion. EKG demonstrated atrial fibrillation with rapid ventricular response and old inferior Q waves. Monitor showed sustained ventricular tachycardia. The patient was admitted for further evaluation, went to the ICU and was placed on phenylepinehrine. Systolic BP increased to 90-100. However, the patient's rhythm degenerated to sustained ventricular tachycardia which was pulseless. The patient was shocked into atrial fibrillation/sinus tachycardia. He was then placed on a lidocaine drip and intubated. He was subsequently placed on dopamine and furosemide. ECHO showed right atrial and ventricular dilation with tricuspid and mitral regurgitation. There was also left atrial enlargement and a suggestion of stagnation of blood in the left ventricle. The patient was anti-coagulated and was also treated with amiodarone and digoxin. Eight days later the patient had an AICD placed, but continued to have PVCs on telemetry post AICD placement. He was eventually extubated and made steady improvement. The patient was discharged on the following day. The study medication was held during hospitalization. No information on whether it was reinstituted.

Patient 0074-010

This 55-year-old male with a history of congestive heart failure, idiopathic cardiomyopathy, diabetes mellitus, CAD, s/p MI, peripheral vascular disease, s/p toe amputation, and s/p left wrist surgery, was admitted for EP evaluation and possible AICD placement after 2 months and 8 days of being on BiDil. The patient has a history of palpitations and non-sustained ventricular tachycardia at home that had not been recorded. Electrophysiologic evaluation. demonstrated inducible ventricular flutter associated with hemodynamic collapse. In addition, there were runs of sustained ventricular tachycardia at 250 msecs. Cardioversion was required for rescue from the sustained episode. An AICD was placed following the EP study. The

subject had a stable post-op course and was discharged 2 days later. The subject completely recovered and study medication was temporarily stopped.

Patient 108-024

This 65-year-old female with a history of congestive heart failure, ischemic cardiomyopathy, hypertension, atrial fibrillation, diabetes mellitus, hyperlipidemia, s/p CVA, mitral valve disease, aortic valve disease s/p MI, irritable bowel syndrome, GERD, glaucoma, amaurosis fugax and osteoarthritis, was on BiDil when she developed weakness and had an episode of syncope and a Holter monitor was reported to show non-sustained ventricular tachycardia. Five months after being on the study drug, she underwent electrophysiologic evaluation. demonstrated easily inducible, sustained, monomorphic ventricular tachycardia with a left bundle branch block, left axis morphology and a cycle length of 200 msecs. This required DC cardioversion to restore to normal sinus rhythm. Following the procedure, the patient was admitted directly to the hospital, and underwent placement of AICD 2 days later. The post procedure course was uneventful. The patient was discharged 1 day later. The subject completely recovered and study medication was temporarily stopped.

Patient 126-001

This 59-year-old male with a history of congestive heart failure, hypertension, diabetes mellitus, ETOH abuse, hyperlipidemia, s/p DVT and chronic renal insufficiency, was on BiDil for 43 days when he was found unconscious in the front of his apartment with a cigarette in his hand. On the ride to the hospital, the patient developed ventricular tachycardia and ventricular fibrillation, and was treated with DC counter-shock two times plus intravenous lidocaine, and was intubated. He responded and upon arrival in the ER, he was placed on dopamine and mechanical ventilation. Heart showed III/VI systolic murmur. EKG showed LBBB. The patient was admitted to the ICU, was treated with intravenous antibiotics and diuretics, and 2 days later, he extubated himself. He was begun on amiodarone therapy. He had reported episodes of nun-sustained ventricular tachycardia while on amiodarone. Eight days after the beginning of events, the patient was transferred to the study hospital, and 3 days later he underwent electrophysiologic evaluation which demonstrated inducible monomorphic ventricular tachycardia with a cycle length of 290 msecs. Patient experienced syncope during this episode and required 1 DC shock to restore sinus rhythm. The patient subsequently had an AICD placed. He was later discharged, completely recovered and study medication was stopped temporarily.

Patient 228-007

This 55-year-old male with a history of congestive heart failure, hypertension, ventricular tachycardia, s/p AICD implantation, hypothyroidism possibly secondary to amiodarone, and apical thrombus, experienced ventricular tachycardia that triggered the firing of his ICD 6 months after being on BiDil. The patient presented to the hospital due the following day and was admitted for further evaluation. Two days later, the patient was hypotensive with BP 76/63 and had complaints of shortness-of-breath and lightheadedness. The patient was hydrated gently and given oxygen, and afterload reducers, beta-blockers, amiodarone and diuretics were held. His blood pressure increased and was in no acute distress. Other lab studies indicated hypothyroidism felt secondary to amiodarone with TSH of 8.40, and levothyroxine was initiated. Seven days after the beginning of events, the patient was considered stable and was

discharged home. The subject completely recovered and study medication administration was temporarily interrupted.

Patient 25-017

This 54-year-old male was on BiDil for 7 months when developed angioedema. Following the morning dose of BiDil, the patient developed shortness of breath, swelling of the tongue and lips and became unresponsive. EMS was called and administered 1 amp D5OW with return of mental status. They also administered diphenhydramine IV. It was noted that the patient was recently switched to a different ACE inhibitor. The patient had not eaten anything that day nor the day before and only consumed alcohol the day before. The patient was brought to the where he was given additional diphenhydramine plus methylprednisolone IV. The swelling of the lips and tongue improved. The patient was recommended to stop ACE inhibitors and refrain from alcohol ingestion.

Patient 032-004

This 63-year-old female was on BiDil for 5 days when she developed angioedema. This was a single episode that was determined to be mild and no action was taken regarding study medication. The subject completely recovered.

Patient 044-005

This 46-year-old male was on BiDil for 6 days when he developed angioedema and light headedness, and was seen at the ER. He was treated with diphenhydramine, dexamethasone, ranitidine and methylprednisolone. The patient improved, was discharged to home, and his study drug was discontinued.

Patient 074-010

This 55-year-old male who was BiDil for 33 days experienced swelling of the face and "hands breaking out" with itchiness of the hands and visited the ER one day later. He had been placed on lisinopril. On exam there was an erythematous rash on the hands and periorbital edema. He was treated with diphenhydramine and prednisone orally in the ER. The swelling improved and rash improved. The subject was told to stop lisinopril, and was discharged. The subject recovered with sequelae and no action was taken regarding study medication.

Patient 121-011

This 31-year-old female who was on BiDil for a little over 10 months presented to the Emergency Room with a complaint of difficulty swallowing for 1.5 weeks but worse on the day of admission. This was associated with a sore throat, runny nose, chills, hot and cold feeling, and a productive cough with yellow sputum. Patient had vomiting for last 2 days. Also has pain in both ribs with coughing and "body aches". She also notes she is talking in a high-pitched voice for the last 5 days.

On exam, there was a hoarse and squeaky voice with swelling of the uvula. The patient was treated with diphenhydramine and methylprednisolone IV. She subsequently improved and was discharged the same day. She was given a prescription for methylprednisolone orally and was told to discontinue her losartan. She completely recovered and no action was taken regarding study medication.

Patient 174-001

This 53-year-old male who was on BiDil for 6 months experienced angioedema of the lips. It was felt that this was secondary to trimethoprim/sulfamethasoxazole that the patient had been

given for an infection. The patient was treated with prednisone. The event ended two days later. The subject completely recovered and no action was taken regarding study medication.

9.6 References

9.6.1 Selected Findings from Literature Referred to in the Review

Figure 6. Mortality from CVD excluding stroke and CHD for 20 mmHg lower BP[9]

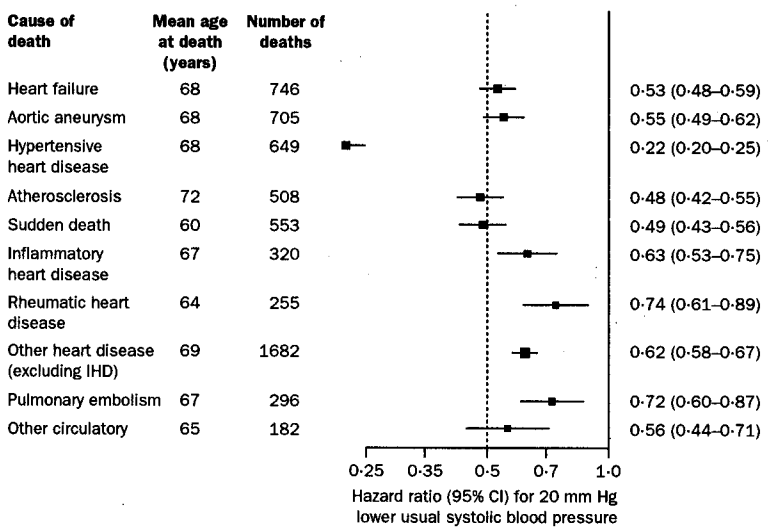


Figure 7: **Mortality from other vascular causes (not stroke or ischaemic heart disease): hazard ratios for 20 mm Hg lower usual systolic blood pressure**

[9] Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13

Figure 7. Effect of hypertension treatment on fatal and non-fatal congestive heart failure in trials comparing old with new drugs[10]

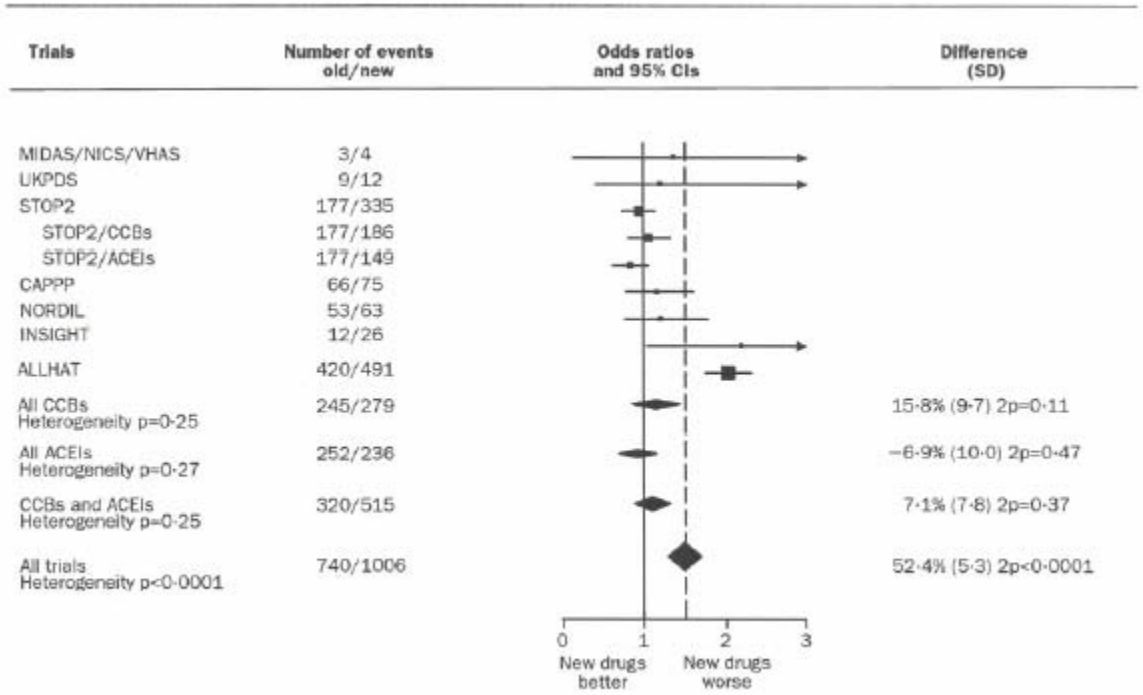


Figure 3: **Effects of antihypertensive treatment on fatal and non-fatal congestive heart failure in trials comparing old with new drugs**

[10] Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13

Figure 8. Effect of increased systolic and diastolic blood pressure by decade age increments on CV mortality excluding stroke and IHD[11]

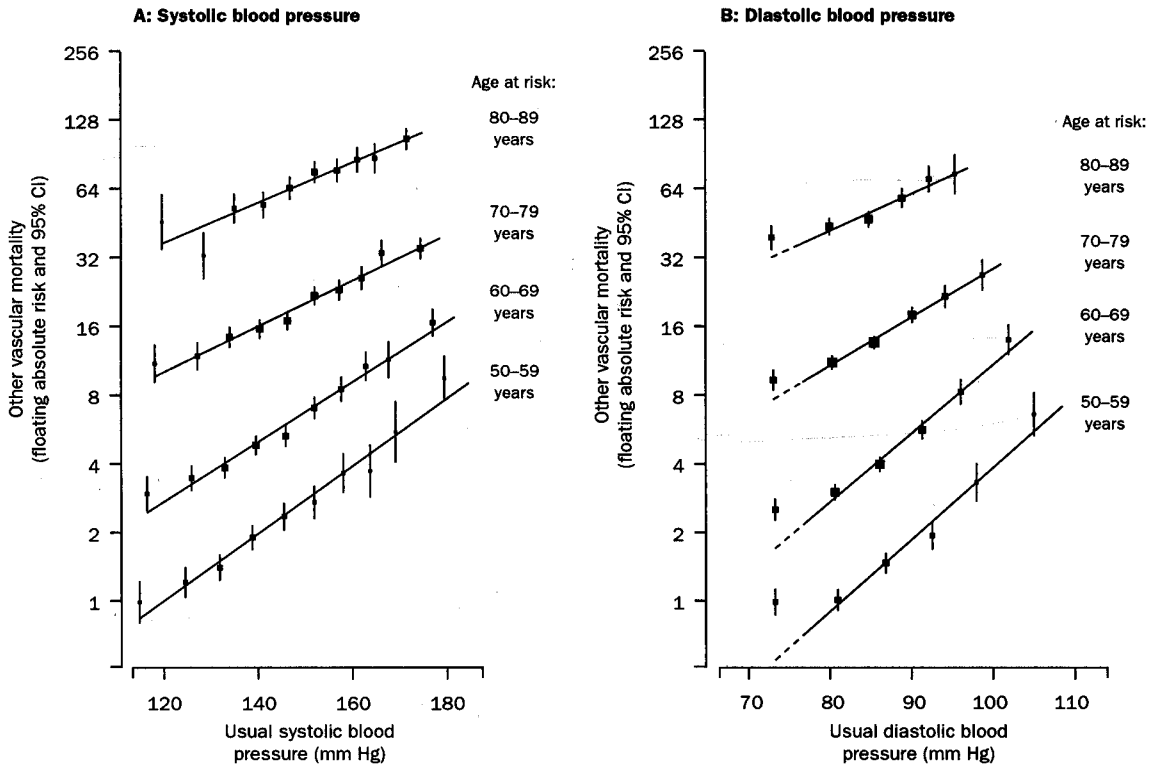


Figure 6: **Other vascular (not stroke or ischaemic heart disease) mortality rate in each decade of age versus usual blood pressure at the start of that decade**
Conventions as in figure 2.

[11] Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13

Figure 9. Relation between systolic blood pressure and cardiovascular mortality and events[12]

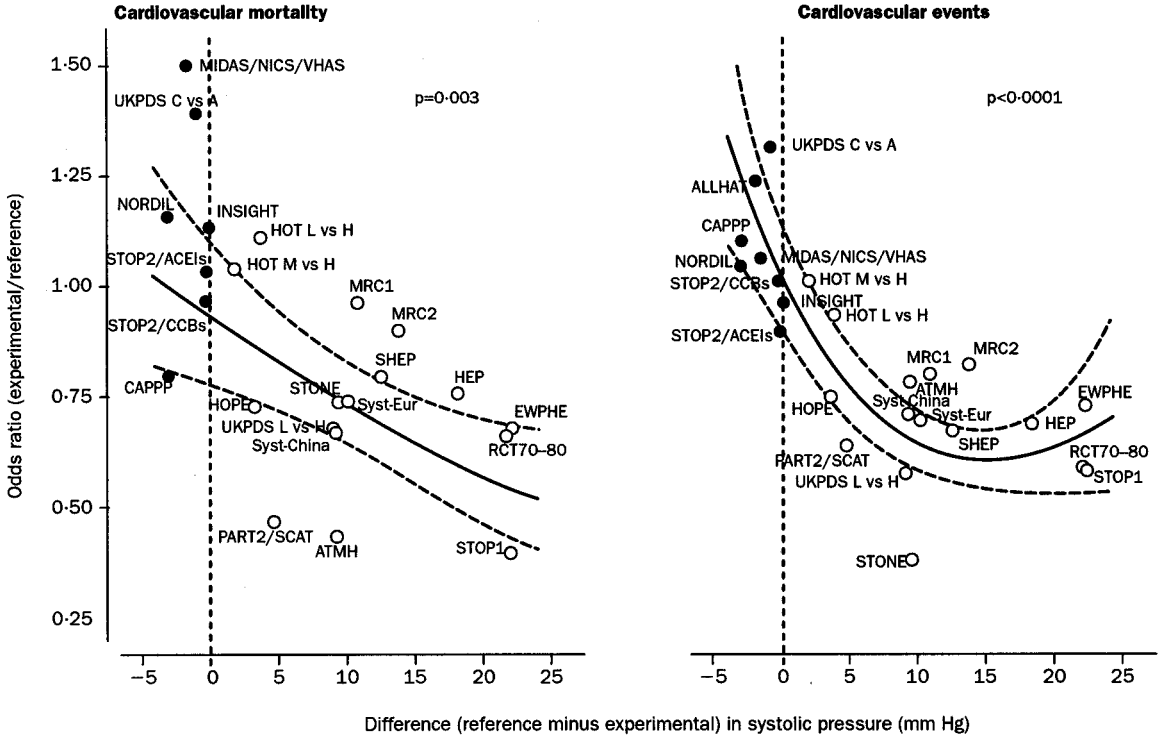


Figure 4: **Relation between odds ratios for cardiovascular mortality and all cardiovascular events, and corresponding differences in**

[12] Staessen, JA, Wang JG, Thijs L, Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001; 358: 1305-15

9.7 Line-by-Line Labeling Review

To be completed separately.

See 8.3 Recommendation on the Label, page 68.